18th Annual Meeting, American College of Chest Physicians
Congress Hotel, Chicago, Illinois, June 5 - 8, 1952

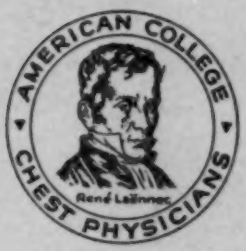
VOLUME XX NUMBER 6

DISEASES

of the

CHEST

OFFICIAL PUBLICATION



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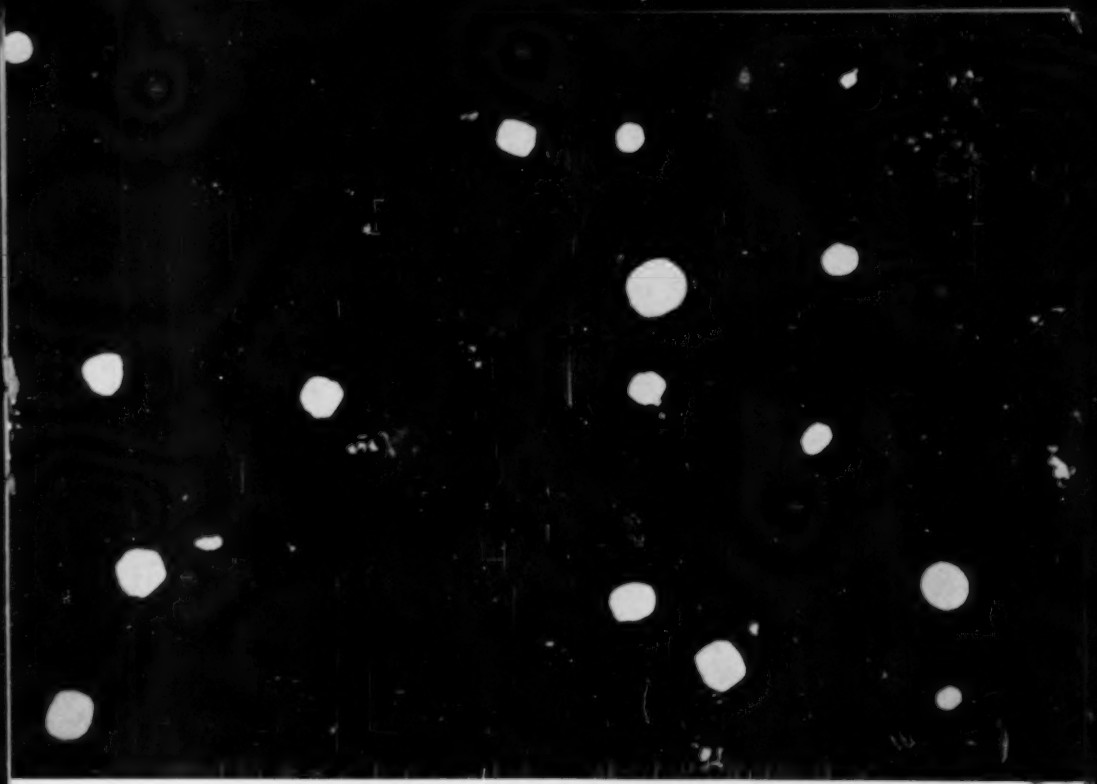

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OF THE

AMERICAN COLLEGE OF CHEST PHYSICIANS

EXECUTIVE OFFICE
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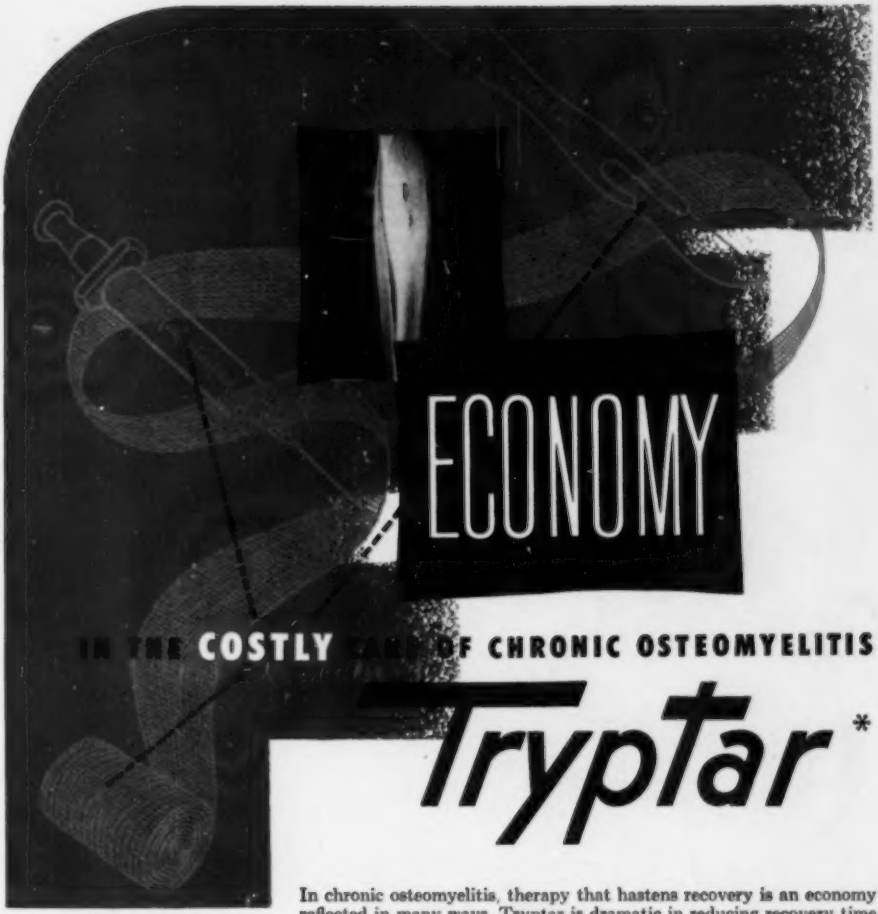

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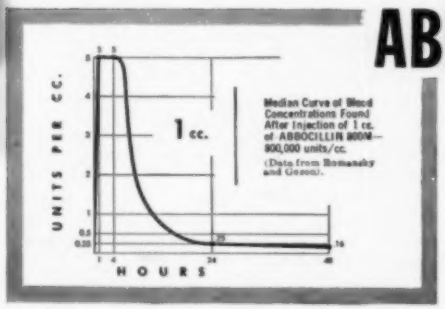

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DISEASES *of the* CHEST

VOLUME XX DECEMBER 1951 NUMBER 6

Intravenous ACTH Therapy in the Treatment of Bronchial Asthma*

MAURICE S. SEGAL, M.D. F.C.C.P.† and
J. AARON HERSCHFUS, M.D.††
Boston, Massachusetts

ACTH intramuscularly is being used in the treatment of many diseases. The drug has to be administered every six hours because of the short duration of the effects of a single injection, regardless of the size of the dose. Resistance suggesting tachyphylaxis, eosinophil escape, allergic and anaphylactic reactions have been observed with ACTH administered intramuscularly.

Sayers et al.[1] administered to two subjects a large dose of ACTH (Armour equivalent of 100 mg. and 50 mg. respectively) intravenously over a one-hour period. In both the metabolic changes effected by ACTH occurred promptly, were maximal by the third hour and had returned to pretreatment levels by the sixth hour. One subject had a shaking chill and fever, the other subject experienced no untoward effects.

Gordon et al.[2] subsequently reported their observations on the effects of continuous intravenous infusion of ACTH. A small dose of ACTH administered in this fashion to humans was able to maintain increased adrenocortical activity over a prolonged period of time. Fifty milligrams of ACTH were given in two or three liters of fluid over eight to 24 hours. Measurable responses were prompt, maximal and sustained.

Recently Renold et al.[3] reported their clinical and laboratory

*Presented in part at the meetings of the Florida (April 22, 1951) and Illinois (May 23, 1951) Chapters and the ACTH Symposium at the Annual Meeting of the American College of Chest Physicians, Atlantic City, New Jersey, June 8, 1951.

†Clinical Professor of Medicine, Tufts College Medical School; Director, Department of Inhalational Therapy, Boston City Hospital.

††Research Fellow in Medicine, Tufts College Medical School.

TABLE I

PATIENT	— ACTH THERAPY —		— — EOSINOPHILS — —	
	Total Dose (mg.)	Duration (days)	Before ACTH	Lowest During ACTH
1. C.T.	92.5	4	2481	27
Results: Excellent remission for 6 weeks. Severe asthma 2 weeks later requiring hospitalization and second course of i.v. ACTH.				
Comments: Four previous courses of i.m. ACTH, total 8640 mg. I.v. ACTH was preceded by 440 mg. ACTH i.m. with little effect. Resistance to i.m. therapy and eosinophil escape promptly overcome with i.v. therapy.				
C.T. (2nd admission)	160	9	14	0
Results: Excellent remission for 1 week.				
Comments: Improvement less prompt than observed with first course.				
2. H.O'R.	110	9	250	0
Results: Complete remission for 2 weeks followed by gradual exacerbation.				
Comments: Two previous courses of ACTH i.m. required 720 mg. with good results and 600 mg. with poor results. Effective results were obtained with much smaller i.v. dose.				
3. J.G.	145	3	94	6
Results: Good remission from status asthma. Low grade fever and persistent severe bronchitis required intensive antibiotic therapy to control.				
Comments: Two previous courses of ACTH i.m. required 800 and 620 mg. Good clinical results with i.v. ACTH but developed anxiety state.				
4. E.W.	120	6	—	—
Results: Good partial remission (5 weeks).				
Comments: Intensive therapy (no ACTH) for 48 hours had little benefit. Good improvement with small doses of i.v. ACTH.				
5. J.O.	10	1	636	243
Results: Good partial remission (5 weeks).				
Comments: Became symptom-free with minute dose of i.v. ACTH.				

TABLE I (Continued)

PATIENT	— ACTH TREHAPY —		— — EOSINOPHILS — —	
	Total Dose (mg.)	Duration (days)	Before ACTH	Lowest During ACTH
6. W.L.	40	2	175	19
Results: Excellent remission from bronchial asthma for 5 weeks. Persistent bronchitis required intensive antibiotics and iodides for control.				
Comments: Had 5 day febrile episode beginning 2nd day after course of i.v. ACTH. Etiology not determined.				
7. J.K.	210	7	—	—
Results: Completely symptom-free for 6 weeks. Required no therapy in remissive state.				
Comments: Seriously ill, non-responsive to all treatment prior to i.v. ACTH.				
8. N.K.	130	4½	738	0
Results: Symptom-free for 6 weeks. Low grade bronchitis persisted, ultimately responded to therapy.				
Comments: Striking improvement from bronchial asthma after 12 hours of i.v. ACTH.				
9. L.F.	100	5	819	7
Results: Excellent remission (1 week).				
Comments: Two previous courses of ACTH i.m. required 845 mg. with 1 week remission and 520 mg. with 5 months excellent and 3 months partial remission.				
10. C.L.	55	4	969	6
Results: Excellent remission.				
Comments: Prolonged hospitalizations during June and July in past 3 years. Complete remission with i.v. ACTH in 5-day hospitalization.				

*Follow-up to date, July 1, 1951.

observations with intravenous ACTH infusions in a large series of patients. They pointed out that the longer the period of the infusion, the longer the effects of adrenocortical stimulation last, that only a small daily dose (20 mg.) is required for maximal effect and that a daily eight-hour infusion continued for more than three days may result in a constant, maximal level of stimulation from the third day on.

Mandel et al.[4] administered ACTH intravenously to 25 patients; four of these were treated for bronchial asthma. The total dose for these four patients ranged from 10 mg. to 88 mg. given over a period of two to eight days. Two patients received the ACTH infusions for 20 out of each 24 hours. One patient received an eight to 12 hour infusion daily and the fourth patient was given intravenous injections every six hours. All four patients had excellent immediate results and no untoward effects from the infusions. The authors concluded that, in comparison with the intermittent intramuscular route, the intravenous route results in a more prompt and complete clinical response, as well as an earlier and more marked change in eosinophil count and in sedimentation rate.

We have described our laboratory and clinical results in the management of severe bronchial asthma with ACTH administered intramuscularly.[5-7] The total dose of a single course of therapy ranged between 240 mg. and 1070 mg. and the duration of treatment from 2½ to 19 days. Since April 1951, we have given 11 courses of intravenous ACTH to 10 patients suffering from severe acute or intractable bronchial asthma. In Table I are listed the particulars about each patient and the treatment. Brief case reports are given at the end of this paper.

Technique

The patient was started on a continuous infusion of 5 per cent glucose in distilled water (three liters per 24 hours, 30 drops per minute flow), usually with 0.5 gm. of aminophyllin per liter of fluid. ACTH was added, 10 mg. per liter, and a total dose of 30 mg. per 24 hours was given for one or more days. As improvement occurred, the dose was usually decreased to 15 or 10 mg. per 24 hours until satisfactory recovery was observed.*

The total dose of a course of therapy ranged from 10 mg. to 210 mg. of ACTH and the duration of treatment from one day to nine days.

*Recently we have modified our routine as follows: After the second day of *continuous* ACTH i.v. therapy, the ACTH is administered only in the first liter of fluid daily. The infusion of glucose, with or without aminophyllin, is continuous.

Results

In Table I are the results of treatment. Seven patients became symptom-free for variable lengths of time, followed by partial remissions. The others had only partial remissions. There were no complete therapeutic failures. To date (follow-up from one week to 10 weeks) there have occurred two severe recurrences, Case 1 (C.T.) about eight weeks after i.v. ACTH treatment, and Case 2 (H.O'R.) about three weeks after treatment. All other patients have remained in good partial remission up to the present, the longest period being eight weeks.

Discussion

Several advantages are obvious at once when ACTH is administered by continuous intravenous infusion rather than by intermittent intramuscular injections. A more rapid therapeutic effect may be observed and this apparently is maintained throughout the 24-hour period. The total dose is about one-fifth to one-eighth of that required intramuscularly. Some effects are obtained at an accelerated rate.

Cases 1, 2, 3 and 9 demonstrate the great saving in material and expense when ACTH is given by the intravenous rather than the intramuscular route. Case 2 (H.O'R.) previously had received 720 and 600 mg. of ACTH i.m. which had given her a remission of one month and one week respectively. The intravenous course of ACTH totalled 110 mg. and was followed by two weeks of complete and one week of partial remission. Case 3 (J.G.) had received previously 800 mg. and 620 mg. of ACTH i.m. which was followed by five months and four months respectively of satisfactory partial remissions. The intravenous course of ACTH was 145 mg. and was followed by a good remission to date. Case 1 (C.T.) had received a total of 8200 mg. of ACTH i.m. over five months (three intensive courses and maintenance therapy in between these courses) during which time he suffered three severe bouts of status asthmaticus. During the third course he received a total of 740 mg. of ACTH and this was followed by nine weeks of partial remission. At the outset of his fourth hospital admission, he was given a fourth course totalling 440 mg. of ACTH i.m. without clinical improvement and without effect on the eosinophils. When i.v. ACTH was started, prompt clinical effect and striking eosinopenia were observed. A total dose of only 92.5 mg. was followed by six weeks of complete and two more weeks of partial remission. *This case, moreover, demonstrates that resistance to i.m. ACTH and eosinophil escape was overcome by i.v. administration.*

Case 9 (L.F.) was given i.m. ACTH in August 1950, a total dose

of 845 mg. over 12½ days. She had an excellent remission which lasted eight days only. A second course was given, 520 mg. over five days, which was followed by five months of excellent remission and three months of partial remission. The present course of i.v. ACTH totalled 100 mg. given over five days and resulted in excellent remission to date (six days).

Physiologic effects, particularly "mooning" of the face, weight gain and a sense of well-being, with psychic manifestations varying from elation to anxiety, eosinopenia and subjective clinical improvement were noted quite promptly with i.v. therapy. However we are not prepared to conclude from our small series of cases that the duration of hospitalization will be shortened by using the intravenous route.

Case 3 (J.G.) had a temperature elevation of 100 degrees F. one day after cessation of i.v. ACTH therapy. Several days later he complained of a profuse rhinorrhea and coughing paroxysms which were productive of several ounces of white mucoid sputum in a 24-hour period. The temperature subsequently rose to 102.2 degrees F. The white blood count ranged from 13,000 to 15,000 and the eosinophil count had risen again at this point. The aureomycin, which he had received since admission, was omitted and penicillin was substituted. The febrile episode subsided and his clinical findings improved. It is interesting to speculate that the acute sinobronchitic flare-up was possibly related to the withdrawal of ACTH with subsequent lymphoid hyperplasia.

Case 6 (W.L.) had chills and fever lasting five days after having received ACTH i.v. for two days. He was the only patient who did not receive antibiotics during ACTH therapy. Forty milligrams of ACTH, even though given intravenously, is a small dose; its relation to this febrile episode is not certain.

All of our patients receiving ACTH are placed concurrently on penicillin or aureomycin to protect against the possibility of greater susceptibility to infection which may follow in the wake of ACTH therapy. A persistent type of bronchitis, generally responding to intensive antibiotic therapy, iodides and antihistaminics, has been observed in most of our patients who have received ACTH by both the i.m. and i.v. routes.

Although some clinical and laboratory studies would suggest beneficial effect from ACTH initially in combating infection, on the other hand there are conclusive studies indicating that cortisone and perhaps ACTH may actually depress resistance to infection. Recently this subject has been reviewed most thoroughly by Kass and Finland.[8] These authors also presented evidence suggesting that adrenocortical hormones themselves may be of pathogenic importance in some diseases.

Case Histories

Case 1 (C.T.), a 50 year old white male executive, was well until 16 months ago, when he developed severely progressing bronchial asthma and emphysema. During this period he was hospitalized three times because of severe status asthma and was given three intensive courses of ACTH i.m. Interim daily maintenance ACTH therapy was continued at home for several months. A total of 8.2 grams of ACTH was administered. He appeared to have made an excellent recovery. In January 1951, pulmonary function studies revealed: vital capacity, 5.1 liters; maximum breathing capacity, 92 per cent of predicted normal; an enlarged residual air and total lung volume and a high residual air to total lung volume ratio of 44 per cent (normal, 30 per cent).

His subsequent admission was for severe progressive cough and wheezing which followed a severe upper respiratory infection one month ago. He was admitted on April 2, 1951 in marked respiratory stridor and status asthma. He was treated with bronchodilator sprays, a continuous intravenous infusion of 5 per cent glucose in distilled water plus 0.5 gm. of aminophyllin per liter of fluid, saturated potassium iodide, Demerol and penicillin. Despite these procedures, he grew worse and a fourth course of ACTH i.m., totalling 440 mg. was administered. He appeared to be somewhat improved. The initial eosinophil count was 377/cu. mm. and decreased to 119/cu. mm. in 24 hours; but then rose daily to a high of 2600/cu. mm. on the fifth day of i.m. ACTH therapy. ACTH was discontinued and all other medication was continued, but in 48 hours he was again acutely ill with severe respiratory stridor. The eosinophil count at this time was 2481/cu. mm. In the hope of effecting a better clinical response, as well as a more adequate eosinopenia, he was started on intravenous ACTH. Ten milligrams of the Armour ACTH preparation were added to each liter of the intravenous infusion which had been maintained since admission. He received 30 mg. per 24 hours for the first two days, and 15 mg. per 24 hours thereafter; total dose was 92.5 mg. over four days. Striking subjective and objective improvement occurred within several hours after the i.v. ACTH was started, and he was free from cough and wheezing on the second day. There was striking reduction in eosinophils from 2481 to 611/cu. mm. on the second day, 27/cu. mm. on the third day and 88/cu. mm. on the fourth day of i.v. ACTH treatment. "Mooning" occurred within 24 hours but no other abnormalities were noted. He was discharged symptom-free on April 22, 1951; the eosinophils were 1493/cu. mm. He was placed on maintenance aminophyllin solution per rectum, potassium iodide and antihistaminic drugs by mouth.

In his sixth week of remission, he again required bronchodilator sprays in addition to other maintenance therapy. Two weeks later he developed a severe recurrence of coughing and wheezing and he had to be readmitted in status asthmaticus on June 7, 1951. He was started on a continuous intravenous infusion of 5 per cent glucose in distilled water, three liters per 24 hours, containing 0.5 gm. of aminophyllin and 10 mg. of ACTH per liter. He also was given ether in oil, oxygen, Vaponefrin aerosols and penicillin. He did not become free of severe asthmatic crises until the third day of ACTH therapy. Remarkable improvement was noted on the fifth day. He received a total dose of 160 mg. of ACTH over nine days. The eosinophil count was 14/cu. mm. on admission and became zero the next day; two days after the ACTH, the eosinophil count was 1706/cu. mm. He was discharged well on June 23, 1951.

Case 2 (H.O'R.), a 40 year old housewife, had suffered from continuous progressive bronchial asthma for nearly one year. In December 1950, she was hospitalized because of intractable coughing productive of purulent sputum, and wheezing. For four weeks, she was treated with bronchodilator aerosols, oxygen, penicillin, aureomycin and various other drugs. Nevertheless she progressively grew worse, became stuperous and finally comatose. Bronchoscopic aspiration was performed without benefit. A course of ACTH i.m. was started. During the first 24 hours, she appeared terminal. However, during the second 24 hours she was "alive" and improvement progressed rapidly. She required a total of 720 mg. of ACTH over a 10 day period. She continued to improve for one week after discharge and remained well for a total period of one month.

Then the coughing, wheezing, expectoration and dyspnea recurred and progressed, requiring readmission on February 1951, about eight weeks after discharge. She was treated with the usual therapy for two weeks, during which time her condition deteriorated. A second course of i.m. ACTH was started. She received 600 mg. over an eight days' period. Striking improvement did not appear until the fourth day. She was discharged feeling partly relieved but within four weeks she had to be readmitted for the third time.

Once again she was treated intensively with penicillin, terramycin, bronchodilator aerosols, aminophyllin, infusions, oxygen, etc., over a five weeks period. Despite these procedures she grew worse and again filled up with purulent secretions and became stuperous. On May 4, 1951 she was started on her third course of ACTH, this time intravenously. For the first three days she received a continuous i.v. infusion, totalling 50 mg. of ACTH, then 10 mg. daily for the following six days. She received a total of 110 mg. of ACTH over nine days. By the end of the first 24 hours (20 mg. ACTH), she was slightly improved. After the next 24 hours (about 40 mg. ACTH), she was considerably improved. She was discharged 10 days after i.v. ACTH was started in good remission. A two weeks follow-up revealed complete remission; she felt much better than she ever had before. At four weeks after discharge she again was suffering from troublesome productive cough and dyspnea. These symptoms grew progressively worse. She was readmitted on June 19, 1951, dyspneic and slightly cyanotic. The intern administered adrenalin and Demerol without benefit and she died suddenly three hours after admission. The gross pathologic sections revealed diffuse bronchiolar obstruction, severe emphysema, and a mitral stenosis of rheumatic etiology.

Case 3 (J.G.), a 55 year old grocer, suffering from bronchial asthma for 10 years, had frequent hospitalizations in status asthmaticus. In 1949 he had a sympathetic denervation. In July 1950 he received 800 mg. ACTH i.m. followed by about five months of good remission. A second course of ACTH i.m. was given in December 1950, totalling 620 mg. followed by about four months of partial remission. Four days before present admission, he developed intractable coughing with continuous asthma which could not be relieved by i.v. aminophyllin and Demerol.

On admission May 24, 1951, he was started on a course of continuous infusions of 5 per cent glucose in distilled water, three liters per 24 hours, containing 0.5 gm. of aminophyllin and 10 mg. of ACTH per liter of fluid. In addition he was given aureomycin, potassium iodide and Demerol. Objective improvement was noted in 10 hours. However, on the second day he appeared anxious and nervous and alternatingly depressed. The

ACTH was increased to 25 mg. per liter and he was also given nasal oxygen. This was continued until the fourth day when ACTH was omitted (total dose 145 mg.), because of rather severe anxiety and apprehension. All other medications were continued. The following day his temperature was 100 degrees F. and he ran a low grade fever for several days. After a few days of normal temperature, he developed a fever of 102.2 degrees F. He had a profuse rhinorrhea and recurrence of bouts of coughing productive of mucoid sputum. Sputum culture revealed a gamma streptococcus, and nasal culture revealed staphylococcus aureus and alpha streptococcus. The aureomycin was discontinued and replaced by penicillin. Ten days later he showed good improvement. The vital capacity, which could not be obtained at the time of admission because of severe coughing paroxysms, rose progressively to four liters. He was finally discharged symptom-free on June 22, 1951.

Case 4 (E.W.), a 22 year old female with non-seasonal bronchial asthma since childhood, required daily medication to maintain comfort. She developed an acute asthmatic attack which progressed over a two weeks period despite a host of medicaments, including several i.v. injections of aminophyllin. On admission April 11, 1951, she was in status asthma. During the first 48 hours she was treated with continuous aminophyllin i.v., adrenalin i.m., potassium iodide and chloral hydrate p.o., nasal oxygen and penicillin with bronchodilator aerosols. There was no appreciable improvement. All medication was stopped and she was started on a constant infusion of 5 per cent glucose in water containing 10 mg. ACTH per liter of fluid. She received 30 mg. per 24 hours for two days and 15 mg. per 24 hours thereafter, totalling 120 mg. over six days. She required only one i.v. aminophyllin injection about eight hours after i.v. ACTH had been started. She became comfortable within 24 hours and she was discharged on April 21, 1951, in partial, but good remission. Her partial remission has continued and she feels greatly improved.

Case 5 (J.O.), a 10 year old schoolboy, had bronchial asthma since the age of two years, with exacerbations during spring and fall. The present attack of intractable asthma started three weeks before admission, and was not relieved by bronchodilator aerosols and other medications. He was hospitalized on May 4, 1951, in a condition of chronic depletion, cyanosis and severe asthma. He was treated with Demerol, potassium iodide, aureomycin and a continuous i.v. infusion of 5 per cent glucose in water to which was added 0.25 gm. of aminophyllin and 5 mg. of ACTH per 1500 cc. of infusion. He received a total of 10 mg. of ACTH over 24 hours with striking clinical improvement. The eosinophils decreased from 636 cells to 243/cu. mm. He was discharged on May 11, 1951, symptom-free and was placed on rectal aminophyllin, potassium iodide and bronchodilator sprays, maintaining a partial remission.

Case 6 (W.L.), a 49 year old white male machine-inspector, had been suffering from low grade chronic morning cough for about 25 years. Two years ago he developed non-seasonal bronchial asthma, frequently associated with upper respiratory infections. The past history was negative except for an attack of pleurisy two years ago.

The present acute illness started the day before hospitalization with intense coughing and wheezing which did not respond to aminophyllin, adrenalin and antihistaminic preparations. On admission May 7, 1951, he was started on i.v. ACTH, 10 mg. per liter of 5 per cent glucose in

water with 0.5 gm. aminophyllin. Three liters were administered in each 24-hour period. He received a total of 40 mg. ACTH over 48 hours. The circulating eosinophils decreased from 175/cu. mm. to 19/cu. mm. Potassium iodide, expectorant cough mixture, chloral hydrate and bromides were given as adjuvants. Clinical improvement was striking by the second day; the i.v. ACTH was stopped and rectal aminophyllin solution was substituted. Two days later (fifth hospital day) he developed a fever of 100 degrees F. and he ran a febrile course for five days with temperatures up to 103.6 degrees F., with a concomitant rise in pulse and in respirations. He had profuse perspiration and several shaking chills at the height of the fever. Physical examination was negative, as was also an x-ray film of his lungs. The white blood count ranged between 10,000 and 12,000 with a normal differential count. Blood cultures, cold agglutination tests and other serologic studies were negative. He was given aureomycin for three days without effect on the fever; this was followed by penicillin i.m. every three hours for five days. He made a complete uneventful recovery. At the time of discharge on May 20, 1951, he was symptom-free and this state was maintained at the time of a follow-up five weeks after the noted improvement from i.v. ACTH.

In contrast to all the other patients on i.v. ACTH, he had not received antibiotic therapy during treatment with ACTH. The cause for the febrile episode could not be determined.

Case 7 (J.K.), a 61 year old housewife, had been aware of nasal polypi and chronic bronchial asthma for approximately 13 years. The present illness was characterized by progressive wheezing and coughing over a two week period, and on May 4, 1951 she required hospitalization because of status asthmaticus.

She was first treated with i.v. aminophyllin, adrenalin in oil and barbiturates but failed to respond. She was then started on a continuous i.v. infusion of three liters of 5 per cent glucose in distilled water per 24 hours, containing 1.5 gm. of aminophyllin and 30 mg. of ACTH, and was also given Demerol and oxygen. After 48 hours, she was free of asthmatic attacks and from that time on, she showed rapid improvement. Treatment was continued for seven days; the total dose of ACTH was 210 mg.

She was discharged symptom-free on May 15, 1951. Her vital capacity, which could not be measured at first, was 2.2 liters. Complete remission has been maintained.

Case 8 (N.K.), a 46 year old secretary, has had chronic bronchial asthma since the age of 27, with seasonal variations, due largely to pollens and infections. She suddenly developed an attack of severe bronchial asthma during an acute atypical pneumonia in January 1951. She responded to therapy and remained comparatively well on maintenance treatment until May 1, 1951 when she again developed severe bronchial asthma, relieved only slightly and temporarily by i.v. aminophyllin injections and Demerol. Hospitalization was necessary two days later.

Upon admission she was given a continuous i.v. infusion of 5 per cent glucose in water with 0.5 gm. of aminophyllin per liter, and Demerol, 50 mg. s.c. every eight hours. When there was no evidence of improvement after 12 hours, ACTH was added to the infusion (10 mg. per liter). She received 30 mg. per 24 hours of ACTH over a period of 4½ days; a

total dose of 130 mg. ACTH. Aureomycin, 500 mg. p.o. every six hours was also given. Improvement was observed within 12 hours. Puffiness of the face was noted after 48 hours of continuous i.v. administration of ACTH. On the fifth day, the lungs were clear and she was discharged symptom-free on May 10, 1951. The eosinophils decreased from 738/cu. mm. to 3/cu. mm. 24 hours later and to zero the next day. On the day of discharge, the eosinophil count was 163/cu. mm. Complete remission has been maintained.

Case 9 (L.F.), a 52 year old housewife, had suffered from bronchial asthma for about eight years. In August 1950 she developed a progressive severe attack of bronchial asthma and she became refractory to epinephrine, aminophyllin and antihistaminics. She was given 845 mg. of ACTH i.m. with complete remission which lasted only eight days. She was given a second course of ACTH i.m. totalling 520 mg. Clinical remission was complete and lasted five months, followed by three months of partial remission. During the spring of this year, she again became refractory to epinephrine and aminophyllin and was given two courses of oral cortisone, about 500 mg. each, with temporary improvement.

The present admission (June 15, 1951) was necessitated by severe intractable bronchial asthma of six days duration, not relieved by i.v. aminophyllin and Demerol. She was started on a course of continuous infusions of 5 per cent glucose in distilled water, three liters per 24 hours, containing 10 mg. of ACTH per liter. She also received potassium iodide, Demerol, sedatives, penicillin and i.v. aminophyllin for severe attacks of asthma. She became free of asthmatic attacks in about 24 hours, but coughing and wheezing did not disappear until the fifth day of i.v. ACTH therapy. The total dose of i.v. ACTH was 100 mg. The eosinophils decreased from 819/cu. mm. (control level) to 19/cu. mm. in 24 hours, 7/cu. mm. on the fourth day, and rose to 200/cu. mm. two days after ACTH was discontinued.

While this patient had previously reacted to iodides with rashes and edematous eyelids, she was able to tolerate large doses of potassium iodide this time while receiving i.v. ACTH. She was discharged symptom-free on June 22, 1951 and has remained well one week to date.

Case 10 (C.L.), a 67 year old painter, has had bronchial asthma since the age of 30 years, with severe exacerbations during June and July. During the past few years hospitalization for several weeks at a time has been necessary during these months because of the severity of the bronchial asthma. Attempts at hyposensitization with June grasses have been unsuccessful.

He was hospitalized on June 26, 1951 because of severe bronchial asthma which had failed to respond to adrenalin and aminophyllin i.v. He was started on a continuous i.v. infusion of 5 per cent glucose in distilled water to which was added 10 mg. of ACTH per liter. In the first 24 hours, he received a total of 25 mg. of ACTH, and 10 mg. in one liter of fluid daily for the next three days, totalling 55 mg. of ACTH.

Striking improvement was noted 16 hours after the infusion was started. The eosinophil count on admission was 969/cu. mm. and decreased to 6/cu. mm. the next day. The vital capacity, which could not be obtained on admission because of dyspnea, improved progressively to 2.8 liters at the time of discharge. He was discharged symptom-free on the fifth hospital day, and remission has been maintained to date.

SUMMARY

1) Eleven courses of intravenous ACTH by continuous infusion were given to 10 patients with severe bronchial asthma.

2) The total dose ranged between 10 mg. and 210 mg. given over a period of one to nine days.

3) Seven patients obtained excellent remissions lasting up to six weeks. The others obtained partial remissions only. There was no complete therapeutic failure.

4) One patient who demonstrated clinical resistance and eosinophil escape with i.m. ACTH responded promptly to i.v. ACTH.

5) Antibiotics should be administered concomitantly, particularly to those patients with bronchitic manifestations, to combat possible depressed resistance to infection produced by ACTH.

CONCLUSIONS

The use of i.v. ACTH offers an effective means in the treatment of severe bronchial asthma. The total dose, and thus the cost to the patient, is cut to one-fifth to one-eighth of that required when ACTH is given intramuscularly. It appears to be an effective way of sending an infant on a man's errand. This route of administration is particularly effective when the patient demonstrates resistance to i.m. ACTH or eosinophil escape. No allergic reactions were observed in this small but intensively treated series. Two patients had febrile episodes following shortly after ACTH therapy, the pathogenesis of which could not be determined.

Occasionally, one observes following the cessation of ACTH therapy a rapid recurrence of respiratory difficulties. We have attempted to prevent such recurrences as well as to prolong the remissive state by the administration of large doses of oral* or rectal aminophyllin and antibiotics when indicated.

*Large doses of oral aminophyllin were given without gastric distress in the form of a proprietary tablet (Dainite®) kindly supplied by Irwin, Neisler Co., Decatur, Illinois.

RESUMEN

El uso del ACTH intravenoso ofrece un medio efectivo en el tratamiento del asma bronquial severo. La dosis total, y por consiguiente el costo para el paciente, se reduce a de una quinta a una octava parte de la requerida para administración intramuscular. Parece ser una forma efectiva de que un niño haga la tarea de un adulto. Esta ruta de administración es especialmente efectiva cuando el paciente muestra resistencia al ACTH intramuscular, o persistente eosinofilia. En esta serie pequeña pero que recibió tratamiento intenso, no se observó ninguna reacción alér-

gica. Dos pacientes tuvieron episodios febriles poco después de la terapia con ACTH, cuya patogenia no pudo ser determinada.

Ocasionalmente se observa, al suprimir la terapia con ACTH, un rápida reaparición de los trastornos respiratorios. Hemos procurado evitar tales reapariciones y prolongar el estado remisivo por medio de la administración de dosis grandes, orales o rectales, de aminofilina y antibióticos, cuando son indicados.

RESUME

L'utilisation de l'A.C.T.H. par voie intraveineuse est un moyen efficace pour lutter contre les formes graves de l'asthme. La dose totale est abaissée au cinquième ou au huitième de celle qui est nécessaire quand l'A.C.T.H. est employé par voie intramusculaire. Cette diminution des doses entraine une diminution parallèle du prix de revient du traitement. Ce mode d'administration est particulièrement efficace quand le malade se montre résistant à la voie intramusculaire ou ne devient pas éosinophilique. Les auteurs n'ont pas constaté de réactions allergiques. Deux malades eurent des épisodes fébriles suivant de peu le traitement par l'A.C.T.H., la pathogénie n'en a pu être élucidée.

Dans certains cas, on a pu observer la rapide réapparition des troubles respiratories après cessation du traitement par l'A.C.T.H. Les auteurs ont essayé de prévenir de telles rechutes et de prolonger la période de rémission. Ils ont utilisé dans ce but de fortes doses d'aminophylline par voie buccale ou rectale et des antibiotiques quand ils étaient indiqués.

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Coccidioidomycosis*

A Review

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Coccidioidomycosis is an infection caused by the fungus Coccidioides immitis, Rixford and Gilchrist, 1896.[1] The primary type is usually a self-limited pulmonary infection. It may have no symptoms or may be characterized by a prostrating influenza-like illness with chest pain and may have associated skin lesions of erythema nodosum. These lesions may be disseminated with generalized infection or may localize in skin, bones, or joints.

The first case of this disease was described in 1892 by Posada[2] and also by Wernicke,[3] the case originating in the Argentine. Rixford[4] in 1894 reported a case from San Francisco. In 1900 Ophuls and Moffitt[5] reported another case and identified the causative organism as a fungus. There are other occasional scattered reports of coccidioidal granuloma or the disseminated disease through the literature. In 1934, Stewart and Meyer[6] isolated the organism from the soil in a San Joaquin Valley ranch. The real clinical picture of the disease as we know it today, however, was first well described by Ernest Dickson,[7,26] a Stanford University Pathologist, who thoroughly discussed the acute form "Valley Fever." After his untimely death, Dr. Charles E. Smith, formerly of Stanford and now of the University of California, School of Public Health, continued these studies and has made noteworthy contributions[8-20] in developing coccidioidin suitable for skin testing, in studies on the pathology of the disease as well as its immunology and epidemiology.

There are numerous clinical contributions, but to William A. Winn[21,22] we are indebted for really comprehensive clinical studies. He has sustained his interest, enthusiasm, and productivity in this field to date.

From the surgical standpoint, Burton H. Cotton[23] of Los Angeles has recently reported on a series of 31 cases of pulmonary coccidioidomycosis treated surgically. This is the largest carefully followed group reported to date and gives a comprehensive picture of the present surgical possibilities.

After Dickson[7] reported his original studies in 1937, attention was called to a previous item by Gifford[24] in the Annual Report

*Presented at the First International Congress on Diseases of the Chest, Rome, Italy, September 20, 1950.

of the Kern County Health Department for the fiscal year 1935-36 reporting a similar group of cases.

There has been much elaboration and development of specific points briefly mentioned in Dickson's original report but, in the five cases he carefully studied and reported on at that time, not much has actually been changed from the picture he then described. Dickson goes on to state that this febrile disease has been recognized in the San Joaquin Valley of California for many years and is locally called "Valley Fever." He gives the clinical characteristics of the disease and states that while patients in this area are numerous they do not seem to be described in the literature, probably because Valley Fever rarely, if ever, has been considered to be a cause of death. He then goes on to describe a laboratory infection in a medical student and four patients seen in consultation, all of whom had local exposure in the San Joaquin Valley. These patients were all diagnosed by finding the organisms in the sputum. An intracutaneous test with an extract of the organism is described, and he concludes that this test is specific and of diagnostic value.

Coccidioidomycosis is a fungus infection which should not be confused with coccidiosis, a protozoan disease infecting the intestinal tract of animals and man.

In culture, Coccidioides immitis occurs in two characteristic forms. On solid media it has a white cottony appearance in young cultures and, as these age, they frequently become pigmented and chlamydospores are abundant. This saprophytic phase is the one occurring in nature. Injected or inhaled by animals the sporangia form. These spherules constitute the parasitic phase of coccidioides. According to Smith,[13] the hyphal spores become rounded and have doubly refractile walls. The protoplasm is divided by cleavage planes and endospores are formed. The endospores may be arranged radially around the periphery of the spherules or may pack the spherule. When the spherule is mature, the endospores are liberated by rupture of the spherule wall. The endospores develop into mature spherules and repeat the endospore-spherule cycle within the animal host. The size of the spherules commonly ranges from 10 to 60 micra, the endospores being 2 to 5 micra in diameter. When the infected animal dies or the spherules are outside the body, germ tubes push out from the endospores or spherules to produce the hyphal (saprophytic) phase. Either the mycelial saprophytic phase or the sporangeal parasitic form can be maintained indefinitely without altering the characteristics of the organism. There is certain work that suggests that the parasitic phase is really the response of the organism to the relatively unfavorable animal environment in which it has assumed

a form optimal for reproductive purposes. There have been no consistent cultural or morphological strain differences ever established. Strains may vary in pathogenicity to laboratory animals but there is no correlation with the type of human infections from which they were isolated nor have strain differences been noted with skin testing antigens. Growth requirements of the organism are simple and it flourishes in a wide variety of media. It survives for years in soil and will withstand a wide range of temperatures. The way the organism multiplies in nature is unknown. It is suggested that while rodents[25] constitute an animal reservoir the clinical and epidemiological evidence seems to definitely show that the infection in man is acquired by the inhalation of chlamydospores blown about in dust. With spores present in the soil, one would expect rodents to be infected even as cattle, sheep, dogs and man are, and while the distribution of the fungus in nature is definitely restricted, no reason can be given. It seems to be clear that the usual portal of entry is the respiratory tract. Occasional instances have been reported of entry through abrasions but most skin lesions are multiple, the result of blood-borne disseminations. The disease is not acquired by ingestion as the fungus does not survive in the intestinal tract. Chlamydospores develop into spherules in the lung producing a pulmonary infection. X-ray films at this time may be negative, may show hilar enlargement or may show extensive pneumonitis. From laboratory infections and from known single exposures, from two days to three weeks after symptoms develop, that is, 10 days to six weeks after exposure, sensitivity to the filterable products of coccidioides develops. This sensitivity increases in degree. While at first the patient may be sensitive to only a 1 to 100 dilution of coccidioidin, within a week he may react vigorously to 1 to 10,000.

Again, according to Smith,[13] shortly after sensitivity is established, often the patient will develop humeral evidence of infection demonstrable by precipitation and complement fixation tests. In most patients, the infection is successfully localized. The individual may be left with a small circumscribed lesion or, more often, nothing at all may be seen. Sensitivity to the appropriate skin testing antigen remains demonstrable evidence of infection as in tuberculosis. But, again, as in tuberculosis and by contrast, the humeral antibodies are relatively transient. Small amounts of pleural effusion may form at this stage and occasionally an extensive effusion may be present.

Cohen[27] from the Kern General Hospital has done much work on this disease and in 1949 reported "95 per cent of the cases of primary lesions are in the respiratory tract. The complement fixation indicates active or progressive disease while the positive pre-

cipitin test indicates recent infection. The longer the coccidioidin skin test remains positive, the better is the prognosis." In this series, 90 per cent of the pulmonary lesions (also including cavities) showed complete recovery. Erythema nodosum was frequent (20 per cent) while an exudative pleuritis was seen only occasionally. In that endemic area, 5 per cent of the erythema nodosum seen in children was not due to coccidioides.

From 60 cases seen in soldiers, Rokolsky and Knickerbocker[28] in August 1946 reported a pulmonary x-ray study. They divided these x-ray manifestations into seven classifications.

1. A nodular lesion, no definite characteristics regarding size or density or with regard to outline or location. This lesion must, of course, be distinguished from tuberculosis and metastatic or alveolar carcinoma, from neurofibroma or neoplasm of the chest wall and pleura.
2. A peribronchial fibrosis.
3. Confluent consolidations.
4. Hilar adenopathy.
5. Pleural effusion.
6. Cavity formation which may be characteristic in that its thin wall may be easily overlooked if the plates are not of good quality. Such an isolated, thin-walled cavity is usually quite annular, frequently without other x-ray evidence of disease and is always suggestive of coccidioidomycosis if tuberculosis can be ruled out.
7. Bilateral nodular dissemination.

They go on to show also how their cases were diagnosed in the following six ways:

1. History of exposure, 100 per cent.
2. Erythema nodosum, 30 per cent.
3. Positive x-ray findings, 85 per cent.
4. Positive coccidioidin skin test 1 to 100, 80 per cent.
5. Positive serology (both precipitin and complement fixation), 86 per cent.
6. Microscopic diagnosis:
   a. Blood eosinophilia, 25 per cent.
   b. Isolation of the spores in the sputum, 6 per cent.

A study by Sweigert and Turner,[29] in 1946, states that, in their patients showing symptoms, 80 per cent had pain in the chest, 50 per cent had cough and 61 per cent had fever. Many more of these had been febrile before they entered the hospital, however. In their 77 cases, the x-ray manifestations were that 70 per cent showed pneumonitis, 23.3 per cent adenitis, 7.8 per cent cavitation, 5.2 per cent nodules, 2.6 per cent pleural effusion, 2.6 per cent negative x-ray. They also confirm previous observations by

Smith and others that the warning signs of impending dissemination are persistently high blood sedimentation rates, a rising complement fixation titer and a falling precipitin titer. The intradermal coccidioidin skin test, under these conditions, may become negative.

In endemic areas, a number of studies have been done in regard to the incidence of erythema nodosum or erythema multiforme. Evidence seems to be clear that these skin manifestations are a sensitivity phenomenon similar to that of other infections and of some drugs. The lesions appear when the peak of allergy has just developed. A coccidioidin skin test at this time would frequently show reaction identical with the prevailing type of skin lesion. As one gains increased familiarity with the disease, the percentage of these acute manifestations is probably in a range of 2 to 5 per cent. The classical coccidioidal granuloma, the first type of lesion described in this disease in man, occurs from the dissemination of a pulmonary infection. It is rather rare, probably not being more than 0.1 per cent of all infections. After involving the lung, the spherules may be carried by the blood or lymph to other parts of the body, where they continue to multiply, such as the meninges, skin, bones, joints, subcutaneous tissue, lymph nodes or any other organ. Dissemination usually occurs in a few months or even weeks after the infection is acquired. After the acute phase is over, the risk of dissemination, never great, is almost negligible. Much work on this has been done by Smith and his associates in connection with a large number of young soldiers brought into these endemic areas, which otherwise were ideal training grounds for certain military operations. This evidence indicates that one infection confers a rather solid immunity (as borne out by animal studies). Practically all residents of most important endemic areas have been infected. Infection in laboratory workers is the rule rather than the exception but exogenous reinfections have never been proven in these groups even though new arrivals in the same environment undergo infection. This disease conforms to a biological pattern in that the infection is exceedingly common in its endemic area, with completely unapparent infections in the vast majority. Clinically typical prostrating illnesses are common but the severe disseminated granulomas are quite exceptional. The pathology of the acute primary infection in man has never been described as the infection is never fatal in this stage, and it has never been possible to examine such a patient who has been the victim of accidental death. Biopsies of erythema nodosum lesions have revealed no differentiating tissue reactions. Information is being obtained from surgical specimens, however, and, of course, at autopsy. Mostly these lesions resemble a tuberculous lesion and

histologically are obviously granulomas. The only specific diagnostic factor is the finding of coccidioidal spherules.

Knowledge of the distribution of coccidioidomycosis is not entirely complete. It is known in the Southwestern portion of the United States, in certain parts of California, Arizona, Mexico and West Texas. Studies to date seem to show that as far as the United States is concerned, in Texas the area extends along most of the Mexican border. It includes a large part of Western Texas and covers Southern New Mexico and Southern and Central Arizona. The Southern tip of Nevada and of Southwest Utah is also included. In California, the most highly endemic area is the Southern San Joaquin Valley. Further North in Merced and Modesto it seems to be rather spotty. The endemic area along the West side of the San Joaquin Valley extends farther, approximately to Tracy, into and over the Coast Range. While the infection is seen in the city of Paso Robles to Santa Barbara and Ventura, the area is not heavily contaminated. There are spotty endemic areas in San Diego County, San Bernardino and Riverside Counties in Southern California.

The disease is endemic in the Argentine, extends from the dry subtropical areas in the North to Patagonia. In the area of Rio Negro, however, reported by Negroni[30] et al. in 1949, intradermal tests with 1 to 100 coccidioidin in school children gave positive results varying from 1 to 10.26 per cent in various towns and rural areas. Hospital patients in Buenos Aires gave 8.1 per cent positive reactions. This author has explained the variation in various almost contiguous areas, by the direction of winds being from West to East in Patagonia and the Central Pampas. This also explains the incidence of the disease, as determined by intradermal tests in the Province of Buenos Aires.

Gomez[31] has recently reported on the Paraguayan Chaco area. In the skin testing of 548 men in two hot and dry, windy dusty areas, where 291 tests were done, there were 71 or 24.3 per cent positive and 220 or 75.7 per cent negative. All of the positive reactors had been residents more than 10 months. In a third rainy area where 250 men were tested, only 5 or 2 per cent were positive and 245 or 98 per cent were negative.

Smith[15] and co-workers in 1946 reported on the effect of the seasons and dust control on coccidioidomycosis, showing that at camps in the endemic area with dust control during the dry and dusty season, a markedly lessened incidence of both infection and disease resulted.

While cases are reported from many isolated areas, such reports do not establish that the disease is endemic in that area. The fungus may be carried on dusty clothing or on agricultural prod-

ucts. We know of definite incidence of the disease in people who have never been in the endemic area. A woman, for example, acquired the disease by brushing her husbands dusty clothes who had just returned from a field trip in an endemic area.

Montessori[32] in 1947 reported on three patients in Italy who had definite diagnoses of coccidioidomycosis and who had never been out of the country. One, a girl of 14, in Naples in 1949 developed pulmonary lesions with cavity; secondly, a man of 40 in 1929 who worked in a Naples grain silo handling materials from an endemic area; third, a woman in Naples in 1933 had glands only. These three patients lived in a coast town and one worked directly with imported grain. Instances of disease such as this can easily be labeled as tuberculosis and consequently diagnosis not established.

Brazil[33] was reported incorrectly as an endemic area. This grew out of the confusion of Paracoccidioides brasiliensis with Coccidioides immitis.

The incubation period of initial coccidioidal infection has been ascertained to be between one to four weeks, generally 10 to 16 days. Knowledge of this is a real assistance in fixing sites of infection and thus demarcating endemic areas. One important aspect is that of communicability. The usual portal of entry being the respiratory tract and as the light small chlamydospores are blown about easily in the air, human infections have resulted from contaminated clothing and dusty products such as cotton and grain. However, spherules of the parasitic phase are not contagious. This seems to be quite clear. There is some controversy about this point at the present time in American literature due to certain studies by Rosenthal[34,35] of Chicago, who stated he could infect guinea pigs by depositing spherules in their bronchial tree. While this is possible with very large doses, there is much epidemiological evidence that this does not happen in man. Even in families where a person with a coccidioidal cavity had constantly numerous spherules in his sputum, no other members of the family became infected even though the contact was intimate and over a long period of time. Such instances can be multiplied many times. A good study on this point has been made by Bass[36] of New York and co-workers on families of veterans with residual cavitary coccidioidal lesions. In reviewing the subject, Berke,[37] in March 1950, sums up by concluding, "It would appear to be correct to say that coccidioidomycosis in man can be considered non-contagious."

Rosenthal[34] also felt, in studying the fate of spherules in the sputum exposed out-of-doors, that according to his preliminary studies the vegetative form of Coccidioides may develop out-of-doors, especially in earth exposed to the sun and in the shade

without soil. The spherules were seen most frequently in the sputum samples kept in the shade without earth and least frequently in the sun with earth. The out-of-doors condition in which both phases of the fungus were seen most frequently was in the shade without earth. The fungus was seen least frequently of all in specimens exposed to the sun without earth and the vegetative form was rarely seen after 30 days, but the parasitic or spherule phase was evident up to 240 days of exposure. He concluded that viability of the spherules was of very low order under the conditions of this experiment.

The infectivity of the chlymadospores is tested further by seasonal distribution. Studies in the endemic area[8] demonstrated that the peak of the incidence of primary infection is in the dusty season while the ebb is in the winter during the few months of rain. Positive skin tests in the endemic area are almost universal. Some Arizona Indian groups show better than 94 per cent reactors.[38] The longer the residence in an endemic area the greater the proportion of infections. In Kern County, Gifford[39] and her associates found the percentage of coccidioidin reactors in school children rose from 17 per cent for those resident less than one year to 77 per cent for those 10 years or over. Aronson's[38] work on the Arizona Indians shows also that there were few positive skin reactions under the age of two years but, coincident with the close association of the child with the soil, the incidence leaped almost to adult figures.

In a study done in the Alameda County Institutions in 1939, Kimball[40] found in 526 routine admissions that were tested:

COCCIDIOIDIN

	No. Patients	Positive	Per cent
Non-tuberculous	259	37	14.3
Tuberculous (Proved)	267	46	17.2

Percentage of hospital admissions, 15.7 per cent positive to coccidioidin.

Further breakdown of these patients regarding sex is as follows:

COCCIDIOIDIN

	No. Patients	Positive	Per cent
Non-tuberculous Male	145	29	20.0
Non-tuberculous Female	116	8	6.9
Tuberculous Male	105	19	18.1
Tuberculous Female	59	6	10.1

We see that there is no apparent significant difference between the non-tuberculous and the tuberculous patients in the number of skin reactors. The higher sex incidence of reactors would be expected in the males. The sex variation appears to be similar in both tuberculous and non-tuberculous groups.

Symptomatology of Primary or Initial Coccidioidomycosis

Many infections, of course, are completely asymptomatic. Others seem to have mild respiratory symptoms which cannot be distinguished from the common cold. There are all gradations, of course, from subclinical infections to severe prostrating illnesses.

The symptoms of this disease as seen in an army hospital in an endemic area of Arizona are well described by J. Gompertz,[41] one of my confreres and an excellent observor, who describes his experience as follows:

"Aside from the usual upper respiratory infections, coccidioidomycosis ranks next in the days loss of duty. Many people walk right through their infections and never know they have it, as evidenced by over 40 per cent of the men in the field reacting positively to coccidioidin.

"The typical hospital case comes in with chest discomfort or pain, a fever of 101 to 102 degrees, may or may not have cough, has no physical signs in his chest and about 20 per cent show erythema nodosum. Sometimes this latter will appear after a week in the hospital as it did in both one of the other doctors and myself. Sedimentation rate will be elevated, usually as high as 20 mm. in one hour by Cutler's method. The chest x-ray findings may be anything from zero to involvement of a whole lobe. In the characteristic x-ray findings there is a wide patch extending out from the hilus with often some large hilar glands seen. We do not find the reported eosinophilia here. The average length of hospitalization is about 21 days. There may be residual malaise for several weeks after that. I have noticed in several patients, usually the severe ones, considerable pain along the tendons, particularly behind the knees but also in the wrists or the ankles. This is not in the joints.

"How do we make the diagnosis? Sometimes it is not easy. However, we become suspicious when the above average picture presents itself. Then if the coccidioidin test changes from negative to positive which it may about the end of the first week, we are more certain. After a week or so, we draw 20 cc. of sterile fasting blood and have it examined by precipitin and complement fixation tests.

"Most cases clear up completely. Negroes are very much more ill than the whites. We have had four disseminated cases, all

Negroes; three of these are dead and the fourth soon will be. No treatment is as yet effective in stopping the disseminated case. The others clear up on bedrest."

This is an excellent summary of the disease as seen in the young male adult who has not previously been living in an endemic area and is suddenly brought into contact with the chlamydospores.

Outside of dissemination and granuloma formation there are two complications we particularly look for. The first is pleurisy with effusion. There may be hardly any systemic symptoms, the fluid may be small in amount but occasionally it may be marked. It should be treated as one treats tuberculous pleural effusion.

The other complication has to do with pulmonary parenchymal lesions which may be nodular or may cavitate. The nodular lesions frequently have not been recognized unless x-ray films were taken before convalescence. They may appear at a later date on survey films when the chest is x-rayed for some other reason and cause much confusion, may be difficult to differentiate from tuberculosis, from malignancy, or from any of the numerous diseases which may give single coin-like shadows on the x-ray film.

Another complication is that of pulmonary cavitation which is usually single though can be multiple. There is generally no physical sign when the cavities form. The cavity will frequently appear after acute symptoms have subsided. It apparently develops in one of the areas of consolidation.

In a study in regard to the pathogenesis of coccidioidomycosis with special reference to pulmonary cavitation Smith[19] and co-workers in 1948, on 274 cases with pulmonary cavities, conclude that coccidioidal pulmonary cavitation may develop in an area of pneumonitis or in a residual lesion some months after a primary infection. Patients with cavities rarely disseminate their infections, appearing to possess an effective immunity mechanism. Frequency of cavitation in unapparent coccidioidomycosis is not known. The cavitation incidence in army hospitalized cases of coccidioidomycosis ranges from 2 to 8 per cent.

Coccidioidal etiology of these 274 pulmonary cavities was verified by recovery of the fungus in 40 per cent, positive serology in 49 per cent, with positive coccidioidin and negative tuberculin in 11 per cent. Double infections, tuberculosis and coccidioidomycosis, were seen in seven of the group. In none was the coccidioidal infection progressive and in only one was tuberculosis progressive. The relatively benign nature of these cavities is indicated by the fact that in the military patients three-fifths of the cavities were incidental discoveries and only two-fifths of the diagnoses resulted from symptoms. In civilians, however, nearly three-fifths of first x-rays were taken because of hemoptysis which, however,

rarely is a real menace. Ninety per cent of the cavities were single and 70 per cent were located in the upper chest. A coccidioidin skin test was the first diagnostic step. Approximately 10 per cent may require coccidioidin stronger than 1:100. A few may be negative even to 1:10 but frequently this is due to misreading. Where serology is negative, and the tuberculin test is positive, the diagnosis can be established only by recovering the fungus from the sputum or by tracheal or gastric lavage. In three-fifths of the sputum-positive patients with coccidioidal cavities proof of the etiology could also be established serologically, when positive fixation of complement was usually only to a low titer in distinction to the high titer characteristic of disseminated infection. Even while cavities were forming, decline in titer of complement fixation and slowing of the sedimentation rates were noted. Three-quarters of the sedimentation rates reported to them were normal. These workers feel that when treating cavities one must realize that while many cavities close quickly a considerable portion may remain open for many years, rarely producing serious health problems. Bedrest doubtless aids in closing cavities early in their evolution, but has limited value later. The risk of dissemination being negligible and the possibility of contagion remote, drastic intervention should be reserved for specific indications. Phrenic interruption sometimes succeeds in closing even long established cavities. Pneumothorax may be used in selected cases but not with peripheral cavities because of the hazard of creating bronchopleural fistulae. Lobectomy, wedge resections or simple excision of the cavity have been successfully done. The high level of immunity in patients with cavities eliminates hazard of dissemination or even local extensions as long as bacterial infection is prevented.

This, of course, is in direct contrast to such problems in pulmonary tuberculosis when exactly the opposite situation presents itself and the tuberculous cavity acts as a direct focus for the local dissemination of the tubercle bacillus. Smith goes on to say that, while coccidioidal cavitation and spontaneous hydropneumothorax are admittedly undesirable, they are much less of a hazard than similar appearing tuberculous lesions and incomparably less dangerous than disseminating coccidioidal granuloma.

We are indebted to Cotton[23] for a report of 31 cases of pulmonary coccidioidomycosis treated surgically. Cotton divides the complications of pulmonary coccidioidomycosis into:

1. Fibrosis of varying degrees of parenchymal infiltration.
2. Coccidioma (using this term to represent the circumscribed density occurring in the lung parenchyma, a coccidioidal granuloma comparable to a tuberculoma and indistinguishable both by x-ray and anatomically).

3. Dissemination.
4. Pleural effusion.
5. Bronchiectasis. (Study by bronchoscopy and bronchography have shown that bronchiectasis is a common sequela of pulmonary coccidioidomycosis.)
6. Cavitation.

Of these six complications, cavitation presents the greatest problem both in prognosis and treatment. The course of the cavities may be divided into acute and chronic phases. An acute cavity may appear with a parenchymal infiltration and disappear completely in the resolution of this infiltration. The typical chronic cavity appears apparently with minimal or no zone of fibrosis about it. The minimum period between these two phases is usually from six to eight weeks with entire lack of correlation between the extent of the parenchymal involvement during the acute phase and the development of cavitation. Cotton states that complications occurring in the medically treated or untreated cavities are:

1. Giant cavity.
2. Secondarily infected cavities.
3. Rupture of cavity with:
   a. Spontaneous pneumothorax.
   b. Empyema.
   c. Bronchopleural fistula.
4. Non-expansile lung.
5. Hemoptysis:
   a. Continued.
   b. Severe.

In all the 31 cases he described, the diagnosis was confirmed by one or more of the following conclusive laboratory methods:

1. Spherules in the sputum.
2. Complement fixation tests.
3. Culture.
4. Guinea pig inoculation.
5. Pathological specimen.

It was noted that the diagnosis of coccidioidomycosis is sometimes easier in vivo than on examination of the pathologic specimen. The coccidioidal cavity which, in the acute phase, allows recovery of the spherules from the sputum, may lose its identity in the presence of a superimposed infection of either tubercle bacilli or a pyogenic organism. Types of surgery done on these 31 cases were:

1. Pneumonectomy 5
2. Lobectomy 12
3. Segmental lobectomy 8

4. Rib resection with decortication	5
5. Decortication plus thoracoplasty	1
Total	31

These patients stand surgery remarkably well. In Cotton's series, 28 of the 31 underwent operations for cavities, only six had operations for empyema, five of whom had cavity resections, and three operations were performed to rule out the presence of carcinoma. In one patient the rapid destruction of the lung parenchyma under medical management alone made the operation an emergency. In another patient, there was concern over surgical intervention because the blood titer was in the dessimination range. In spite of the fact that a cavity was removed and decortication performed in the presence of a coccidioidal empyema, no clinical dissemination occurred postoperatively and the blood titer fell. Three cases were complicated by tuberculosis in addition to coccidioidomycosis. The only death in this series was due to a coronary occlusion several days following operation. It has been their experience, as pointed out also by Winn,[22] that the coccidioidal cavity can at times be closed by collapse therapy, as in tuberculosis. In Cotton's cases, however, where medical treatment was employed, the results had been unsatisfactory. Postsurgical examination of the specimens revealed two causes for the failure of collapse therapy: first, the cavity although appearing thin-walled by x-ray actually was composed of a dense fibrous wall which could be obliterated with difficulty by direct manual pressure; second, dense adhesions were present from the cavity wall to the thoracic cage. The rationale of surgical removal in such cases seems clearly established. Close analysis of these data would lead one to feel that suitability for operation should be determined without regard to the etiologic nature of the pathologic condition or whether the disease was in a dormant or active phase. We should view the complications of pulmonary coccidioidomycosis from the mechanical standpoint only. Cotton's results certainly substantiate the conclusion that the medical status of the disease has little effect, if any, on the indications for operation, the choice of operative procedure or the post-operative results. This illustrates also the difficulty in differentiating some lesions by any means short of incision, a coccidioma from a tuberculoma, a hamartoma or both primary and metastic carcinomatous lesions.

Surgical opinion may differ, however. Melick[42] in 1950 reported on an attempt to tabulate the then known cases of pulmonary coccidioidomycosis treated by excisional surgery. Inquiries were sent to all members of the American Association for Thoracic Surgery as well as to certain other individuals. Replies were

received from 224 physicians representing 37 states in the United States, nine localities in Canada, as well as replies from Hawaii and Sweden. Many of these doctors reported several cases in which apparently the diagnosis had not been made previous to surgery. Surgeons, by and large, feel that persistent longstanding granulomatous cavity is occasion for resection. There were 98 incidences reported of excisional therapy for pulmonary coccidioidomycosis. The indications were persistent cavitation, recurrent hemorrhage, productive cough, suspicion of neoplasm, granuloma, failure of the lung to expand following spontaneous pneumothorax, inability to make the diagnosis and residual cyst. Complications were few; those reported were empyema, bronchopleural fistula and recavitation in the remaining portion of the lung. Three deaths following excisional surgery were reported.

Commenting on this survey, Winn[43] properly sums it up from the medical standpoint in stating that "I am inclined to believe the surgeons are somewhat overdoing resection for this disease. Perhaps the indications for resection have to be more sharply defined. The existence of cavitation per se should not mean pulmonary resection but under certain circumstances surgical removal does become necessary."

Since pulmonary resection has become such a relatively safe procedure, especially segmental resection or lobectomy, under the umbrella of antibiotics and since there is no other disease in which I would prefer to leave a cavity in the lung, and since the chance for repeated hemoptysis or secondary infection of the coccidioidal cavity is substantial, I personally prefer to see such cavities surgically removed if they fail to close under medical treatment.

We believe the coccidiomas or the coin-like lesions, the solid nodules in which a clinical diagnosis cannot be reasonably made, should always be explored and removed and thus definitely establish their etiology because some of them may represent malignancy. In disseminated or progressive disease, dissemination may well first be confused with early tuberculosis, with the exception that in coccidioidomycosis abscesses are often subcutaneous and likely to form early. Removing the pus-like material from these abscesses establishes the diagnosis by microscopic examination or by culture. Occasional cases of localization in various portions of the body are reported, but these are far from common and usually resemble, in many respects, tuberculosis. Coccidioidal meningitis is an infrequent single cause of death in the white race. It runs a rapid course; there is no known treatment.

In differential diagnosis, the mild primary infections resemble a common cold. When erythema nodosum occurs the diagnosis

should not be difficult if there is a high index of suspicion. In the more severe cases generally the diagnosis will be pneumonia; it can resemble tuberculosis or lung abscess. In most instances, unless there are skin manifestations or complications, the diagnosis is not made.

Even in endemic areas, the appearance of erythema nodosum per se is not diagnostic of coccidioidomycosis but, of course, in those areas Coccidioides is by far the most common cause of that manifestation. We must then turn to the laboratory for confirmation. From the clinical standpoint, the most valuable aid is the coccidioidin skin test.[20,44-46] For a long time, coccidioidin, which resembles tuberculin in its manufacture and its use, could only be obtained from Smith's laboratory. Now it is commercially available from the Cutter Laboratory, Berkeley, California. The material consists of a number of strains of coccidioidin grown on asparagine synthetic medium which was developed by Long and Seibert for purified protein derivative. For coccidioidin, 2.5 per cent glycerole is added. The coccidioidin is diluted to 1 to 100 concentration for routine testing. This dilution, if kept sterile and refrigerated, retains its potency for over six months. Undiluted coccidioidin, according to Smith,[18] remains potent indefinitely or at least as long as nine years.

Hassid[48] and co-workers in 1943, reported on An Immunologically Active Polysaccharide Produced by Coccidioides Immitis which consists of units of galacturonic acid, glucose, and some unidentified sugar. A nitrogenous compound apparently other than proteins is associated with the polysaccharide. This polysaccharide gives a skin reaction in sensitive individuals. If obtained by regeneration from the acetyl derivative it no longer produces this skin reaction. Both the original polysaccharide and that obtained from the acetylated derivative give positive precipitative reactions.

The test itself is done exactly as the tuberculin test, using 0.1 cc. of the solution intradermally. It is read in 48 hours and induration over 5.0 mm. is positive, but erythema is of no significance. This reaction denotes previous infection. It gives no indication, of course, of when the infection was acquired. No reaction indicates no previous infection (or immunity) with the exception of disseminated disease in which the coccidioidin reaction is frequently weak or absent. On the other hand, erythema nodosum patients are extremely sensitive. Strong reactions do not flare up infections. In the higher concentrations, there may be some cross reactions to other fungi as, for example, histoplasmosis. A change from no reaction to a reaction is definite proof of infection, recalling that it takes one to two days up to 10 to 14 days for allergy

to be established. The skin test is, therefore, a useful screen. It does not activate a quiescent infection though occasionally it may precipitate erythema nodosum. It does not stimulate humeral antibodies nor interfere, therefore, with the significance of the serological test. There is no cross sensitivity between tuberculosis and coccidioidomycosis as far as skin testing is concerned. Smith emphasizes the fact that demonstration of a change from negative to a positive test, however, is almost as diagnostic as recovery of the fungus.

Smith[20] and his associates discuss the occurrence of cross reaction to histoplasmin in coccidioidal infection. They go into the matter in great detail stating that they had considered coccidioidin very specific. The known endemic area of the United States being confined to the arid Southwest, a serious and discordant note was the experience of Furcolow and Nelson in an orphanage in Ohio where a considerable number of positive reactors were discovered to coccidioidin. They found few positive reactors with dilute coccidioidin but a large number with concentrated material. Up until 1941 when Smith began his systematic coccidioidin survey at a San Joaquin Valley Army airfield, he had observed no difficulty in interpreting the tests. At this time, they realized that coccidioidin did evoke cross reaction in persons coming from areas extended through the central United States. They found some definitely positive coccidioidin tests among groups of soldiers who had never before been West of the Rockies and in whom the test had been performed too soon for them to have acquired local infection. Emmons discovered that the haplosporangium was present in Arizona giving cross reactions with coccidioides. This did not explain all the findings. Antigen was, therefore, prepared from histoplasmin toxilatum. This same histoplasmin was used by Aronson in skin testing in his Arizona survey on non-tuberculous pulmonary calcifications. Certain cross reactions may occur with histoplasmin. In some 3,376 healthy persons negative or equivocal to coccidioidin, 26 per cent reacted to histoplasmin with occasional positive coccidioidin reactions in individuals who had no opportunity to acquire coccidioidal infections. These were found exclusively in a group of histoplasmin reactors. The stronger the histoplasmin sensitivity, the more frequent and large is the nonspecific reaction to coccidioidin. The authors finally concluded that histoplasmin appears to have limitations due to its cross reactions but used in an appropriate relative strength it, and coccidioidin, are valuable in the diagnosis of the specific organism causing a pulmonary lesion.

There are three possible errors in a coccidioidin test:

1. Reading the test too soon or too late.

2. Using glassware in which other biologicals like tuberculin have been absorbed.
3. Contaminating the diluted coccidioidin.

In addition, there may be difficulty in reading the test because of injecting an insufficient amount of coccidioidin or of injecting it subcutaneously instead of truly intradermally. If either occurs, the injection should be immediately repeated.

Serological Tests: Using coccidioidin as an antigen, Smith has been able to demonstrate precipitins and a fixed complement. He states that in unapparent or mild primary infection these humeral antibodies are rarely demonstrable. Generally the more severe the infection, the higher the titer, particularly the complement fixation. Patients with progressive disseminated infections usually have complete fixation in serum dilutions of 1:16 to 1:256 or even higher. They may, however, have no precipitins. In the severe initial infections, precipitins often are demonstrated to an antigen dilution of 1:40 to 1:200. In a patient with a primary infection which first produced only precipitins, but whose serum later fixed complement to progressively higher titers, we would suspect impending dissemination. Precipitins appear a few days after sensitivity to coccidioidin develops. As has been indicated, complement fixation usually is demonstrable a little later. However, precipitins generally diminish after a few weeks and vanish in a month or two but occasionally they may persist for several months. The higher the titer of complement fixation the longer it tends to remain. After severe infections, fixation may continue for several years. The serological tests may be applied successfully to pleural fluid or to spinal fluid. In patients with few meningeal lesions in which the symptoms are largely due to mechanical and cerebral spinal blocking, the serological tests usually are negative.

Blood Changes: Moderate leucocytosis is frequently present. Eosinophilia running from 4 to 20 per cent may occasionally be found. In the healing stages the proportion of lymphocytes will rise to 50 per cent of the total and the shift to the left in the leucocytes disappears. Differential blood count does have prognostic value in following the course of the infection.

Of greater use is the red cell sedimentation. It is especially of value in interpreting the significance of a positive coccidioidin test. Patients with active coccidioidal infections whether primary or disseminated show accelerated sedimentation. Thus, a normal sedimentation rate in a patient with a reaction to coccidioidin makes it unlikely that a current illness is due to this disease. An accelerated rate does not establish the infection as currently active but indicates the possibility and further steps should be taken to prove or eliminate it. If the primary infection is focalized,

the sedimentation may be close to normal so one may use this test to supplement other criteria in determining activity of the infection. Most patients with old coccidioidal pulmonary cavities have normal sedimentation rates. This test is recommended by Smith to indicate that the lesion is not active even though the fungus may be present in the sputum.

The prognosis of primary coccidioidomycosis, including the patient with cavity, is excellent. Probably not more than one-tenth of 1 per cent of the primary cases disseminate in white individuals. The outlook for females is even better than males.

With dissemination the prognosis is grave. While some cases recover, the dark skinned races rarely recover and the white skinned race but seldom. As far as prevention of the disease goes, there is little to offer. If large bodies of men under military conditions are moved into endemic areas, certain dust control measures may be helpful. This is not very practical on a civilian basis. If the infection itself cannot be prevented, we should turn our attention to prevent disseminat'on. The evidence is strong that dissemination nearly always occurs relatively soon, that is, a few months after infection. It may be that prolonged bedrest in known patients will lessen the risk of dissemination. Study of the complement fixation and precipitin test combined with x-ray studies of the lungs give rather definite and reliable evidence of the course of the disease. The patient with an initial infection should be kept at bedrest until clinical recovery, normal sedimentation rate, regression of x-ray findings, and complement fixation titer indicate the infection is being focalized. If x-ray lesions persist, they should be re-checked periodically to be sure that no cavity develops. It is not practical to hospitalize these people until the lesion completely disappears because it may persist for some years. The presence of cavitation with spherules in the sputum does not indicate danger of dissemination. As a clinician who has had occasion to send to Smith's laboratory blood for precipitin and complement fixation, I have been much impressed with the accuracy of the prognosis especially when these tests are done serially on individual patients.

Certain drugs have been reported from time to time as being effective in some instances, but when control cases are used it is found that they are of no value. A recent study was presented by Cohen, Gifford and Smith[47] on Actidione (Lilly). Dr. George Savage of Upjohn's x-rayed conidia of Streptomyces griseus to obtain a superior streptomycin producing mutant. This resulted in a yield of a different substance called Actidione. This was shown to have anti-fungus properties. Dr. Alma Whiffen showed that Coccidioides immitis was inhibited by Actidione in concen-

trations greater than 1,000 micrograms per milliliter. In treating human infections the drug showed no toxicity in the doses used except some gastrointestinal irritation expressed as nausea and vomiting. It may be administered in enteric coated pills of 10 mgm. dosage to a total of 150 mgm. per day or in doses of 100 mgm. intravenously in a saline drip over a period of some three hours. The clinical results, however, to date have been disappointing.

SUMMARY

Coccidioidomycosis should no longer be considered a rare disease confined to a small endemic area in the Southwestern part of the United States and in the Argentine. A high incidence or 25 per cent of infection occurred in personnel stationed in the endemic area during World War II. A similar incidence probably occurred in non-veteran civilians who traveled in endemic area for business, health, or vacation purposes. Bass[49] points out, "Coccidioidomycosis should be considered in the differential diagnosis of unexplained pulmonary infiltrates especially with nodular densities and cavities which remain unchanged over long periods of time. More widespread use of the coccidioidin skin test will aid in the diagnosis of these coccidioidal lesions."

This disease, then, may be seen in any part of the world. Except for the acute stage, it frequently resembles tuberculosis. In a given patient, when tubercle bacilli are not obtained, coccidioidomycosis should be considered, and its presence or absence determined.

RESUMEN

Ya no debe considerarse a la Coccidioidomicosis como una enfermedad rara, limitada a una pequeña zona endémica en el suroeste de los Estados Unidos y en la Argentina. Una alta frecuencia de infección (el 25 por ciento) ocurrió en el personal militar acantonado en la zona endémica durante la Segunda Guerra Mundial. Una frecuencia semejante probablemente ocurrió en personas civiles que viajaron en la zona endémica por razón de negocios, salud o vacaciones. Dice Bass, "Debe considerarse la Coccidioidomicosis en el diagnóstico diferencial de infiltrados pulmonares inexplicados, especialmente con sombras nodulares y cavernas que no cambian por largos períodos de tiempo. El empleo más general de la prueba cutánea con la coccidioidina ayudará en el diagnóstico de esas lesiones."

Puede verse, pues, esta enfermedad en cualquiera parte del mundo. Excepto por el período agudo, frecuentemente se asemeja a la tuberculosis. En todo paciente en el que no se obtengan bacilos tuberculosos debe considerarse la coccidioidomicosis y debe determinarse su presencia o ausencia.

RESUME

La coccidioidomycose ne devrait plus être considérée comme une maladie rare limitée à une petite zone d'endémie dans le Sud-Ouest des Etats-Unis et de l'Argentine. L'infection frappa jusqu'à 25% du personnel stationné dans la zone d'endémie, pendans la deuxième guerre mondiale. La maladie a probablement frappé dans une proportion semblable les civils qui voyageaient dans la zone d'endémie pour leur travail, leur santé ou leur plaisir.

Bass met en évidence que la coccidioidomycose devrait être prise en considération quand on discute le diagnostic des infiltrats pulmonaires de cause inexpliquée, des densifications nodulaires et des cavités qui restent inchangées pendant de longues périodes de temps. L'utilisation plus répandue du test cutané à la coccidioidine permettra le diagnostic de ces lésions.

Cette affection peut être constatée dans toutes las parties du monde. Sauf à la phase aigue, elle ressemble fréquemment à la tuberculose. Lorsqu'on ne constate pas de bacilles de Koch, on devrait penser à la coccidioidomycose et mettre en oeuvre les moyens de rechercher cette maladie.

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Discussion

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Coccidioidomycosis is a fungus infection having a high morbidity and a low mortality. It is known to occur in humans, cattle, sheep, dogs and rodents, and in many ways mimics tuberculosis.[1]

This disease apparently is most prevalent in warm climates, par-

ticularly in areas where there is no rainfall over long periods with a resultant accumulation of much dust. It was originally seen in the chaco region of South America. Many cases have been reported from California, Southern Arizona, Southern Utah, and New Mexico. There are endemic foci in South America, the Balkans, Italy and India. In the United States new areas were discovered by accident as a result of the setting up of army camps. Undoubtedly there are other areas in the world as yet undiscovered.

New areas cannot be determined except with the use of coccidioidin for skin testing, which brings up the problem of how to supply physicians outside of the United States with the material. It can be obtained from Cutter Laboratories, Berkeley, California, in the diluted form ready for skin testing.

The question of therapy for the residual cavity lesion is very important. As Bass[2] states "One is impressed by its benign behavior. Unlike tuberculosis, spread of the disease to the remainder of the lung fields or dissemination to distant organs seldom if ever occurs. Surgery should be reserved for cases with severe recurrent hemoptysis or spontaneous pneumothorax with empyema."

The lack of contagion is important. There is no known case where the disease was transmitted from one individual to another.

A cure for the disseminated or granuloma form of the disease has not been discovered. Several antibiotic agents have been used but no clear cut results have as yet been reported.

The chest specialist therefore, no matter in what part of the world he may be located, should think of this disease particularly when confronted with pulmonary lesions that are not typical of tuberculosis. The present migrations of people through endemic areas will undoubtedly result in the finding of this disease throughout the entire world.

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Double Aortic Arch*

(With report of a case with a rare type of functioning double arch consisting of a slightly larger anterior right arch, smaller posterior left arch, right descending aorta and left ligamentum arteriosum.)

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Anomalies of the aortic arch have been recognized for over two centuries.[1] Hommel[2] published the first description of a double aortic arch in 1737 and for almost 200 years this group of anatomical aberrations remained a subject of interest primarily to anatomists and pathologists. In 1925 Arkin[3] described the roentgenological findings in patients with a congenital vascular ring. Abbott[4] in 1931, Sprague and his co-workers[5] in 1933 and Herbut and Smith[6] (1943) suggested the possibility of surgical intervention for the relief of symptoms resulting from developmental abnormalities of this type. Robert Gross[7] in 1945 performed the first successful operation for the relief of the disabling symptoms caused by a double aortic arch. He divided the small anterior left arch between the origin of the left common carotid and the left subclavian artery in a five months old baby whose vascular ring was completed by a large posterior right arch which crossed the midline behind the esophagus and joined the descending aorta on the left.

It has been well established that not all patients with vascular rings are subject to symptoms. Numerous cases are on record where the individual with such an anomaly has lived out his normal life expectancy or died from unrelated causes only to have the aortic abnormality accidentally discovered upon post mortem examination.[8-10] On the other hand, in those patients whose vascular ring is sufficiently tight to constrict the trachea and esophagus the symptoms are frequently distressing and progressive. Medical treatment offers no hope of alleviation of the

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symptoms. In this group of patients the outlook is poor and an early demise, usually from pulmonary complications, can be anticipated in most instances.[6,7,10,13,15-19]

A double aortic arch results from the persistence of both fourth branchial arches. The embryological development of the definitive aorta has been clearly described and illustrated by Congdon.[20] His work has been summarized by Blackford, Davenport and Bayley[21] in their consideration of right aortic arches and brief reviews of the embryological background of anomalies of the aortic arch giving rise to congenital vascular rings are to be found in the articles by Gordon,[13] Sweet, Findlay and Reyersbach,[22] and Bahnson and Blalock.[23]

Vascular abnormalities of this type are by no means common but they are not exceedingly rare. Blincoe, Lowance and Venable[8] reported in detail a case of double aortic arch in 1936 and reviewed the literature up to that time. Their case was the twelfth of this anomaly which they were able to verify. Griswold and Young[10] surveyed the literature on this subject in 1949 and found reports of 49 cases which they considered acceptable. In an addendum they mentioned two additional cases observed at the Johns Hopkins Hospital subsequent to the submission of their article, bringing the total number of authentic cases recorded up to that time (December 1949) to 51. Bahnson and Blalock[23] reported three cases in March 1950, but it appears that these three patients were included among the four previously mentioned by Griswold and Young.[10] The latter authors did not cite the report of Potts et al.,[24] but one of the two cases recorded by Potts and his associates[24] had previously been reported by Gordon[13] and it appears highly probable that the second case noted in the account by Potts[24] is identical with the one described by Steinberg.[25] Since Gordon's and Steinberg's cases are included in the collected series by Griswold and Young, the case to be reported herein constitutes the 52nd verified example of this anomaly to be recorded in the literature. The increased incidence of reported cases in recent years is doubtless due largely to improved diagnostic methods. The advances in thoracic surgery in the past few years which have made it possible to apply curative therapy to a variety of congenital cardio-vascular disorders have stimulated renewed interest in all types of these developmental defects. As a result physicians generally are becoming more alert to the possibility of the existence of these abnormalities and when suggestive symptoms are present they are prompt in instituting those diagnostic procedures necessary to establish the nature of the disorder. It seems quite likely that, in the past, fatal cases of congenital vascular rings were not infrequently attributed to thymic disorders or other vague

and undiagnosed lesions, and that their increased occurrence in recent years is apparent rather than real.

Gross and Ware[1] have provided an excellent classification of aortic arch anomalies. Edwards[26] has described and illustrated those anomalies of the derivatives of the aortic arch system which may interfere with the function of the trachea or esophagus. In his comprehensive consideration of vascular rings the various forms which have been observed are diagrammed and discussed. In addition, he has included several hypothetical configurations, which, to his knowledge, had not at that time been reported. After noting that they stood out as distinct possibilities, Edwards commented as follows upon his inclusion of these as yet unobserved forms:

"This is done in the hope that when they are encountered, they will be understood and not be viewed with undue surprise. Furthermore, it is hoped that whoever observes these hypothetical possibilities will be stimulated to place them on record in order that the literature may contain a more comprehensive accumulation of this group of anomalies."

The purpose of this paper is to place on record the report of a case presenting a type of aortic arch anomaly, predicted by Edwards[26] but heretofore undescribed, in which there was a functioning double aortic arch with a somewhat larger anterior right arch, a slightly smaller posterior left arch and a right descending aorta. This case falls into the Group II anomalies of Edwards and differs from the hypothetical type which he has described and depicted only in that the ligamentum arteriosum was situated on the left rather than on the right. The first patient mentioned in the addendum to the article by Griswold and Young[10] presented a configuration that was certainly similar to and perhaps identical with that shown by the case to be reported herein. However, their patient's vascular ring did not produce stridor or dysphagia, its symptoms being due to an associated Tetralogy of Fallot. It is assumed that this is the same case reported later by Bahnson and Blalock.[23] The latter authors' description of the finding at operation do not make the exact anatomical situation in their patient entirely clear. They state that "the innominate was the first branch of the right aortic arch," and that "it gave rise to the left carotid and left subclavian arteries and another vessel which was probably the left vertebral. In addition there was a vessel which descended behind the esophagus and this was thought to be a persistent left aortic arch. Its junction with the aorta could be felt but not seen." The position of the ligamentum is not mentioned nor is it shown in the illustration of the vessels on the left; it was therefore probably situated on the right side.

Case Report

The patient (J. C.), a male infant, was born spontaneously at term on November 18, 1949. His birth weight was eight pounds and he was the third child from as many uncomplicated pregnancies of his 22 year old mother. His respirations were established immediately after birth, but markedly stridorous breathing and cyanosis led to direct laryngoscopy in the delivery room. No abnormality of the upper respiratory tract could be found. Physical examination was otherwise normal.

During subsequent weeks the child was observed to have constant and severe stridor which was observed to be both inspiratory and expiratory in type, with pronounced retraction of the lower sternum, excessive secretion of mucous and intermittent cyanosis. On November 25, 1949 direct laryngoscopy again failed to show any intrinsic laryngeal pathology. Chest roentgenograms were repeatedly negative. The baby took the bottle well but each feeding was prolonged because of shortness of breath. Supportive care consisted of oxygen as needed, steam vapor, and prophylactic chemotherapy.

Persistence of all symptoms gave strong suggestion of the possibility of a congenital vascular ring and in pursuing this clue several fluoroscopic examinations were made with swallows of *thin* barium. Spot films were obtained at the second of these examinations which suggested esophageal obstruction at the level of the aortic arch. The arch appeared to pass to the right. Two additional roentgen studies failed to clearly define the deformity.

On January 27, 1950 the infant was bronchoscoped by one of us

FIGURE 1 FIGURE 2

Figure 1: Lateral roentgenogram of the chest showing marked indentation posteriorly of the barium filled esophagus with forward displacement at the site of posterior compression. The dilatation of the esophagus above the area of constriction is well shown.—*Figure 2:* Anterior-posterior chest roentgenogram with a barium swallow showing lateral compression of the esophagus from either side at the level of the aortic arch.

(C.F.S.). The 3.5-30 full lumen bronchoscope was easily introduced. The larynx was normal. The cords moved in a normal manner and the laryngeal opening was entirely adequate. The upper trachea showed nothing abnormal. Immediately above the main carina, at the level of the aortic arch, the posterior membranous wall of the trachea was markedly displaced forward. Definite pulsation could be seen at the site of the posterior compression. In the same area each lateral wall of the trachea was compressed from without and displaced in a medial direction so that the tracheal lumen on inspiration presented as a triangular opening. On expiration it narrowed to a tiny crevice or minute slit. The bronchoscope could not be passed beyond the constricted point. The bronchoscopic impression was that the patient had a congenital vascular ring, most likely a double aortic arch but possibly an anomalous subclavian artery passing posterior to the esophagus.

Two days later another fluoroscopic examination was done, this time employing a *thick* barium mixture. On this occasion the deformity was clearly visualized. In the lateral projection a marked indentation of the posterior esophageal wall at the level of the aortic arch was seen and the pulsatile character of the mass causing this indentation was clearly apparent. In both the right and left anterior oblique positions marked indentations of the esophageal wall at the same level were observed, while in the A-P view bilateral compression of the esophagus was noted. The esophagus above the point of obstruction was considerably dilated. So tight was the esophageal constriction that the barium would "hang up" for an appreciable interval at the point of obstruction, passing beyond only slowly in a thin intermittent trickle. In addition, what appeared to be two aortic knobs were seen, one on either side, with the left being situated at a slightly higher level than the right. There was no appreciable difference in their size. Close scrutiny failed to clearly establish the position of the proximal descending aorta, but it was the fluoroscopist's impression that it probably descended on the left. Numerous spot films were taken but as on all previous occasions it was prac-

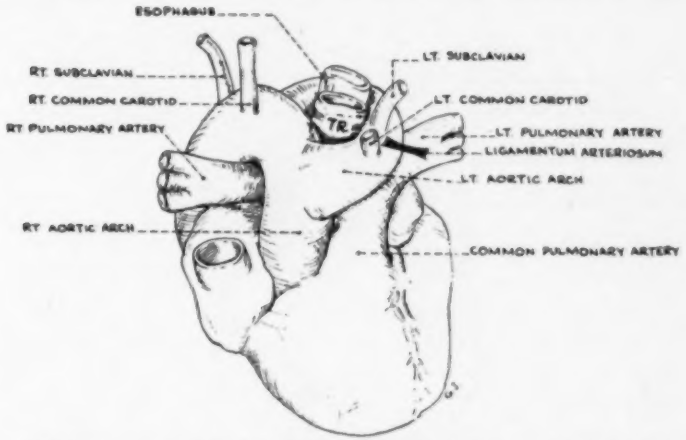

FIGURE 3: Drawing of the vascular anomaly present as seen from in front.

tically impossible to obtain satisfactory roentgenograms in the dyspneic infant who had to struggle vigorously for air at all times (see Figures 1 and 2).

Left thoracotomy was performed (by C.F.S.) on February 16, 1950. Endotracheal ether anesthesia was administered by Dr. F. Cerzosimo. The chest was entered by an incision in the second anterior interspace. An apparently normal aortic arch was seen. It gave rise to the left common carotid and left subclavian arteries at the usual sites. The ligamentum arteriosum ran in the customary fashion from the aortic arch near the origin of the left subclavian to the left pulmonary artery. The ligamentum was quite large but no pulsations could be felt and on palpation it gave the impression of having an obliterated lumen. After dissecting it free throughout its extent, it was doubly ligated with number 20 cotton and divided. It was not patent. It is worthy of note that when the ligamentum arteriosum was divided, the proximal or anterior portion of the left arch moved upward along the trachea a distance of one to two centimeters and the left pulmonary artery retracted downward and forward slightly. This shifting appeared to relieve to an appreciable degree, although not completely, the compression of the trachea. During the dissection of the ligamentum arteriosum the left vagus nerve and its recurrent branch, both of which were situated in the usual anatomical location, were carefully avoided. After mobilizing both of these nerves in the region of the ligamentum, the left recurrent laryngeal nerve was retracted by an encircling ligature of fine cotton which had been looped around it. In this manner it was held well out of the way while the aortic side of the ligamentum was being ligated. In retrospect it is believed that this maneuver constituted a technical error and that it contributed to some degree to the postoperative complications which followed. The descending aorta was not seen in the expected position. Dissection along the aortic arch distal to the left subclavian artery showed that the arch, instead of descending in the left hemithorax as usual, coursed transversely across the mediastinum posterior to the trachea and esophagus and disappeared in the right chest.

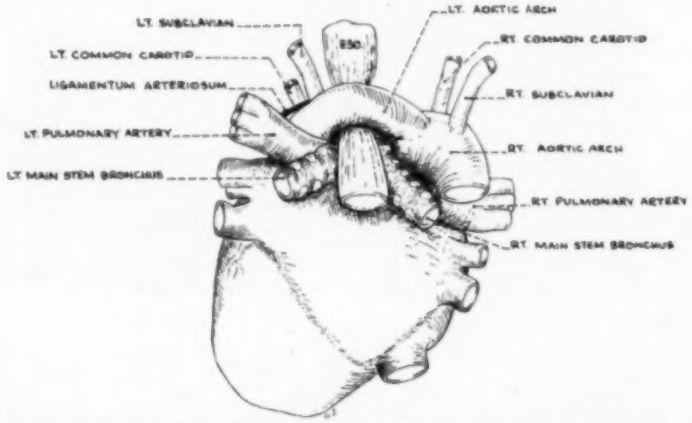

FIGURE 4: Drawing of the vascular anomaly present as seen from behind.

Dissection was then carried out in a medial direction along the anterior portion of the proximal left arch and as the base of the heart was approached a junction between the left arch and a right aortic arch was brought into view. The right arch was seen to be slightly larger than the left, but the difference was not striking. Distal dissection along the right arch was carried out as far as possible through the left thoracic approach. It was possible to demonstrate one large vessel arising from the right arch and coursing cephalad. This was assumed to be the innominate artery, or, more likely in view of the common finding in this anomaly, the right common carotid, although the right subclavian artery could neither be seen nor felt through the exposure available. Immediately distal to the large vessel just described the right arch turned sharply in a posterior direction and on palpation it was determined that it coursed downward and backward. The observations made to this point made it fairly evident that this was a double aortic arch with the left arch being somewhat the smaller of the two. The left arch was freed throughout its circumference and temporarily occluded just distal to its origin and proximal to the point where it gave rise to the left carotid. It was then noted that the carotid and subclavian pulsations were undiminished and the anesthetist reported that the pulse at the temple and in the left radial artery showed no change. It was then clearly established that the left arch joined the right arch in the right chest after passing behind the esophagus and that it could receive blood from either direction. The left arch was therefore triply clamped at the point of temporary occlusion and severed between the middle and distal clamps. The middle clamp was removed and the proximal end of the severed vessel closed by placing two rows of 5-0 black arterial silk sutures in the cuff of the vessel from which the central clamp had been removed. The distal end of the divided left arch was closed by a simple ligature of number 20 cotton placed just proximal to the origin of the left carotid artery. As the proximal clamp was removed following suture of the vessel end, the closed stump was seen to retract well to the right. The ligated distal end when

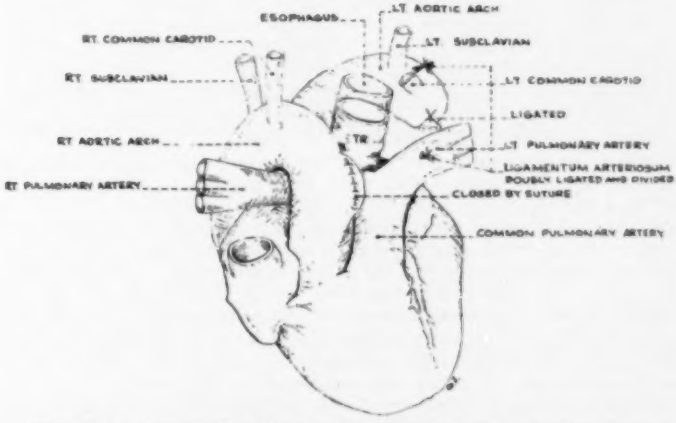

FIGURE 5: Illustration of the situation present following division of the proximal portion of the left aortic arch.

released moved to the left, upward, and backward. Thus the trachea and esophagus were fully released from the tightly constricting vascular ring in which they had been imprisoned and relieved of all external compression save that exerted by the posterior left arch whose distal portion passed from left to right behind the esophagus (see Figures 3, 4 and 5). The chest was closed in the usual manner. The field was dry and drainage was not used. The operation required approximately five hours.

Immediately postoperative, the infant breathed easily and quietly without stridor or sternal retraction for the first time in his life. However, progressive laryngeal edema rapidly developed and a tracheotomy was necessary about eight hours postoperative. Edema of the larynx had been verified by direct observation and in addition a marked paresis, although not a complete paralysis, of the left vocal cord was seen to be present. Considerable technical difficulty was encountered during the performance of the tracheotomy. Done as an emergency in the infant's room, the lighting was poor, the ideal instruments were not at hand, and a trained assistant not present. When the desired tracheal rings had been divided, the first attempt to pass the metal tracheotomy tube resulted in it escaping from the tracheotomy opening and being inadvertently passed into the mediastinum paratracheally rather than within the tracheal lumen. It was immediately withdrawn and re-inserted properly.

On February 17th, the first postoperative day, the baby developed total atelectasis of the left lung. Films showed that the tracheotomy tube was too long and that its tip lay in the right main stem bronchus. It was removed, bronchoscopy performed, and secretions aspirated from the left bronchial tree with resultant re-expansion of the left lung. The tracheotomy tube was shortened and replaced and frequent aspirations by a catheter passed through the tube kept the trachea and right bronchial tree essentially free of secretions. However, within 24 hours the left lung was again atelectatic and remained so despite repeated bronchoscopic and catheter aspirations until the 14th postoperative day. The lung cleared slowly and aeration was complete by that time.

A few days after the tracheotomy the size "O" metal tube was replaced by the size "1" Portex plastic tube in the hopes that the latter would cause less mucosal trauma. However, bronchoscopic observation showed edema of the tracheal mucosa about the tip of the tube and it was necessary to advance it a few millimeters each day in order to maintain an ample airway. In spite of every effort to avoid it, the tube had been advanced to the main carina within a few days.

During the first week after operation, in spite of the atelectasis, the temperature was never higher than 101.2 degrees F. rectally. On the eighth postoperative day the infant spiked a temperature of 102.6 degrees F. and examination showed the signs of fluid in the left chest. Thoracentesis yielded slightly over 100 cc. of milky fluid which contained no pus and which was sterile on culture. Laboratory studies confirmed the clinical impression that this fluid was chylous in nature. A small Pezzer catheter was placed in the pleural cavity through an intercostal trocar opening and underwater seal drainage maintained for five days. Diminishing amounts of fluid were obtained and the tube was no longer draining after the fifth day and was therefore removed.

During the remaining five weeks of the infant's life the plastic tracheotomy tube was removed on innumerable occasions, but efforts to leave it out permanently invariably failed. Immediately following re-

moval of the tube breathing would be perfectly free and without stridor, but slowly progressive respiratory obstruction would ensue and it would be necessary to replace the tube within a few hours.

It was found that oral feeding consistently resulted in aspiration of some of the formula. To obviate the necessity of repeated lavage a length of polyethylene venous catheter material was passed into the stomach, secured in place, and the baby fed through this tube during the remainder of his course. He gained weight slowly but steadily on a formula of half skimmed milk (Alacta) and attained a weight of 10 pounds a few days before his death. Vitamin supplements were supplied with the formula and the child was given a number of small blood transfusions.

During the last week of his life the child ran an irregular spiking fever, reaching a peak of 103.6 degrees F. on April 1, 1950. Much mucous was obtained by suction through the tracheotomy tube (a size 8 ureteral catheter was used for suctioning) and fine rales could be heard over both lung fields. Chest roentgenograms showed no areas of pneumonitis and it was felt that the infant had a terminal bronchiolitis. His maintainence therapy of aqueous procaine penicillin was supplemented by aureomycin and the abnormal physical signs in the chest and the fever promptly abated.

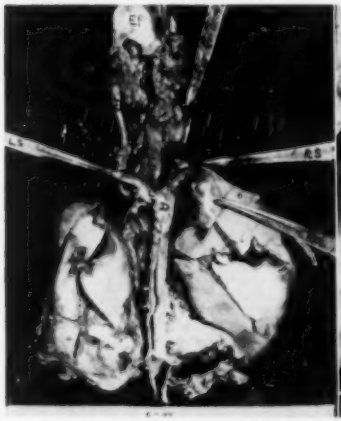

FIGURE 6

FIGURE 7

Figure 6: Autopsy specimen. Heart, lungs, trachea, esophagus and neck organs —posterior view. Legend: (L) left aortic arch. (R) right aortic arch. (D) descending aorta. (RC) right common carotid artery. (RS) right subclavian artery. (LC) left common carotid artery. (LS) left subclavian artery. (EP) epiglottis. (E) esophagus. (G) groove in upper lobe of right lung produced by right aortic arch. (RUL) right upper lobe.

Figure 7: Autopsy specimen. View of the right hemithorax. The anterior rib cage has been removed and the right lung rotated medially and retracted strongly to the left. The anterior right aortic arch, the right common carotid artery and the right subclavian artery, the right vagus nerve (grasped by hemostat inferiorly), the esophagus and the azygos vein and its tributaries are clearly shown. Although it was inadvertently nicked during the course of the postmortem examination and much of the blood which it contained escaped before this photograph was taken, even in its collapsed state a good idea of the great size of the azygos can be gained.

As the bronchiolitis cleared the baby showed marked clinical improvement. It was quite without warning that he developed intractible respiratory failure and died on the 48th postoperative day. Earlier the same day another of the many attempts to permanently remove the tracheotomy tube had been made. The infant breathed freely for some time but after a few hours the usual respiratory obstruction developed and he became quite cyanotic before the tube could be replaced. During this interval there was a minor convulsive seizure. The patient had suffered so many periods of transient cyanosis throughout his life, from which he always recovered upon restoration of his airway, that the cause of his death was not clinically clear. Effective suction had been carried out upon replacement of the tracheotomy tube.

An autopsy was performed. The exact cause of death was not established with certainty. It was stated as asphyxia, due to mucous plugs in both main stem bronchi, plus atelectasis of the left lung and pericardial effusion. Asphyxia, of course, is a clinical rather than a pathological diagnosis. The pathologist reported that both main stem bronchi contained a rather large quantity of blood tinged mucous which he felt could have seriously interfered with respiration during life. However, it was noted that the right lung showed completely normal aeration. The lingula and lower lobe on the left showed patchy atelectasis, but the remainder of the upper lobe showed fairly good expansion. The trachea showed no erosion as a result of the prolonged presence of the polyethylene tracheotomy tube. There was only 15 cc. of fluid in the pericardial sac. A noteworthy finding, whose significance is not entirely clear, was the presence of marked dilatation of the right atrium with associated striking dilatation and distention of the superior and inferior vena cavae and the azygos vein. There was an obliterative pleuritis on the left, the heart was shifted slightly to the left and rotated to the right. The lower sternum, xiphoid process and costal cartilages were depressed. There was atrophy of the thymus gland (due, no doubt, to considerable exposure to irradiation in the course of repeated fluoroscopy and chest roentgenograms. The thymus was noted at operation to be unusually large). The developmental abnormalities of the great vessels described in the operative note were fully confirmed (see Figures 6 and 7). The left arch measured 5 mm. in diameter and right arch 7 mm. The severed ends of the left arch were separated more than one centimeter, suggesting to the pathologist that the encircling vascular ring was rather tight before surgical intervention. The trachea showed no evidence of external compression. The lumen of the ductus arteriosus was obliterated. The post-mortem studies, both gross and microscopic, revealed nothing else remarkable. There were no other congenital cardiovascular abnormalities.

Comment

To our knowledge, this is the youngest patient thus far to undergo surgery for a constricting vascular ring formed by a double aortic arch. The decision to operate upon this infant as soon as the diagnosis was established was based upon the fact that the patient had severe respiratory distress of such a degree that he remained constantly on the verge of exhaustion from the great effort required in breathing. Diligent hospital supervision had

avoided the development of pulmonary complications, but it appeared evident that the slightest respiratory infection would contribute to a fatal issue. We were emboldened to perform a thoracotomy upon this dyspneic infant because ample experience, particularly that of Blalock in his large series of operations for Tetralogy of Fallot, has shown that even poor risk children withstand intrathoracic surgery remarkably well when expertly given anesthesia is available.

In addition to presenting an apparently unique anatomical configuration, this case exhibited several other unusual features. Although the two arches as seen at operation were nearly equal in size, the slightly smaller left arch passed posterior to the esophagus to join the proximal descending aorta on the right. This is contrary to the usual experience as the larger arch, be it right or left, commonly passes behind the esophagus and descends in the opposite chest. Furthermore, the ligamentum lay in the hemithorax opposite that occupied by the proximal descending aorta. Again, this is contrary to the usual finding.

At least two avoidable surgical errors were made during the course of the operation upon this infant. The operation time was too long. The endotracheal tube was in place in excess of five hours and under the circumstances serious laryngeal edema was no more than should have been expected. A prophylactic tracheotomy upon completion of the thoracic operation was considered and discussed. It should have been done under the favorable situation existing in the operating room. We are firmly convinced that the operating time would have been greatly shortened had we used a posterolateral incision, entering the chest through the fourth or fifth interspace or through the periosteal bed of the resected fifth rib. Using this approach the anatomical configuration with which we were confronted would have been recognized, we feel, quite promptly. As it was, prolonged dissection was undertaken before the exposure was sufficient to make the exact situation clear. Finally, traction on the left recurrent nerve, gentle and brief though it was, was both unwise and unnecessary and should have been avoided. It seems certain that that maneuver contributed materially to the unfortunate postoperative chain of events.

There can be little doubt but that the difficulties encountered during the performance of the emergency tracheotomy, and subsequently with the tracheotomy tube, played a major role in the complicated postoperative course. This serves to demonstrate once more that no surgical operation, no matter how minor, should be undertaken electively except under the best possible circumstances as to both material and personnel.

We are not certain as to exactly why this child died. Certainly

at operation, on frequent postoperative bronchoscopy, and at the post-mortem examination it was clearly demonstrated that the compression of the trachea and esophagus had been completely relieved. As a matter of fact, immediately preceding the infant's death we were well pleased with his progress and felt that it was only a matter of time until full function of the left cord would be restored, the laryngeal mucosa again entirely normal, and that at such time the plastic tube could be removed either abruptly or slowly withdrawn a few millimeters each day. In spite of our uncertainty, it is only reasonable to assume that the fatal outcome was intimately related to the necessity of maintaining a tracheotomy tube in place at or near the main carina for a period of seven weeks. Yet even in retrospect we cannot see how this could have been obviated once the complicated situation which we have described had arisen. The many fruitless attempts that were made to permanently remove the tube made clear our desire to discard the tube as soon as its absence could be tolerated. However, the tracheotomy wound would almost completely close in a matter of hours and the tube would be reinserted with difficulty so that the ineffectively coughing infant could be suctioned.

The difficulties which we encountered have been pointed out in order that others may avoid if possible the pitfalls which befell us in the management of this case.

The presence or absence of symptoms associated with aortic vascular rings depends entirely on the availability of space between the two aortic limbs. If there is ample room there will be no constriction of the trachea or esophagus and the patient will suffer no inconvenience. However, if the space is sufficiently small the enclosed structures will be subjected to extrinsic pressure by the surrounding vessels and their compression will give rise to a characteristic syndrome.[14] The cardinal features associated with this anomaly consist of stridor, commonly both inspiratory and expiratory in type, which is markedly aggravated during feeding; dysphagia, which is frequently not outstanding due to the remarkable ability of the esophagus to accomodate itself to extrinsic pressure; attacks of cyanosis; suprasternal, infrasternal, and intercostal retraction and a strong predilection to pulmonary complications.[1,6,7,10,13-19]

The cough is harsh, barking and non-productive unless or until pulmonary complications have supervened. Bouts of coughing may precipitate an attack of cyanosis. Increased cyanosis may occur during feeding and is associated with increased respiratory difficulty. Despite its ready mobility, in lesions of this type the esophagus cannot escape the vascular ring which encloses it.

Swallowing may therefore be difficult and delayed and maintainence of the nutritional status becomes a major problem in the more severe cases. In other infants nourishment may be taken rather readily despite marked respiratory distress. Because of the grave prognosis in cases with pronounced symptoms, the urgent necessity of prompt diagnosis and early surgical relief is apparent. Bronchopneumonia is the most common cause of death,[13-17] but exhaustion, atelectasis, inanition and aspiration of formula are other conditions directly related to the anomaly which have been cited as leading to a fatal outcome.[10]

Once the diagnosis of a double aortic arch has been suspected on the basis of clinical findings, it can be confirmed with reasonable certainty by the employment of roentgen techniques.[3,27] Both roentgenography and fluoroscopic observation should be utilized. In the lateral projection made with a swallow of *thick* barium mixture, the posterior wall of the esophagus is seen to be indented at the level of the aortic arch and the esophagus is displaced forward (Figure 1). At the fluoroscopic screen a pulsating mass can be visualized posterior to the esophagus at this level. In anterior-posterior roentgenograms the esophagus is seen to be narrowed at the level of the arch and compressed from both the left and right sides[27,28] (Figure 2). Classically it is not displaced laterally as it may be by a single right or left arch, but exceptions to this rule have been noted.[3,10] Lateral chest films of suitable technical quality will outline a posterior indentation of the tracheal air column and in the A-P view lateral compression of the trachea similar to that demonstrated in the esophagus can sometimes be seen. These compression defects of the trachea can be shown more clearly by means of a tracheogram made following the instillation of a small amount of lipiodol in the trachea through a catheter or by spray.[1] Bronchoscopic examination will provide confirmatory evidence. The larynx will be found to be normal. Immediately above the main carina, at the level of the aortic arch, the posterior membranous wall of the trachea will be seen to bulge forward. The pulsatile character of the mass giving rise to the extrinsic pressure will be readily apparent. There will also be indentation of both lateral walls of the trachea so that its lumen appears to be triangular in shape. In a young infant the 3.5 mm. bronchoscope can be passed beyond the constricted point only with difficulty if at all. Esophagoscopy in young infants with this anomaly entails an appreciable risk and adds so little to the information that can be obtained by other means that we do not feel that the procedure should be employed routinely as a part of the diagnostic studies. Angiocardiography for a more precise differentiation of these lesions has been suggested.[27,29] It would

seem that under certain circumstances this method of examination would provide useful additional information in the study of a patient with a double aortic arch, although routine employment of the procedure would scarcely appear to be essential. It was of no help in a case reported by Bahnson and Blalock.[23] In a case where exact delineation of the anomaly present appeared to be of paramount importance, it is likely that the vascular pattern could be more clearly defined by retrograde angiography than by any other means and the utilization of that technique where the situation warrants is suggested.

A double aortic arch which gives rise to no symptoms requires no treatment. Since the vascular ring in such cases does not significantly reduce the lumen of the trachea or esophagus, the accidental discovery of a double arch in the course of studies carried out for some other reason is of academic interest only. On the other hand, the possibility of a constricting vascular ring should be considered in any infant who suffers from stridor and dysphagia. Other causes for these symptoms, such as mediastinal tumors, tetany, or tracheal or laryngeal abnormalities should be ruled out by appropriate studies.[13] An enlarged thymus is mentioned only to be dismissed, for in the opinion of most observers that condition is rarely if ever responsible for the symptoms under consideration. Where it has been established that the symptoms present are due directly to the effects of pressure exerted by a vascular ring formed by persistent right and left aortic arches, surgery now offers real hope of permanent relief from the serious and disabling manifestations of the abnormality.[1,2,15,23,24] It is a fortunate fact that this lesion is not frequently associated with other congenital cardiovascular defects. Blalock,[23] Gross,[1,7] and Potts,[24] each of whom has had a wide experience in the surgical treatment of congenital heart disease in infants and children, have encountered only a few examples of double aortic arch. Furthermore, a review of the recorded cases of double aortic arch shows that associated cardiovascular abnormalities are an exceptional finding.[10] The urgency of surgical intervention is emphasized by the studies of Griswold and Young,[10] who analyzed the records of 19 infants under the age of two who had a double aortic arch. All except two of them had symptoms due to the anomaly. Three of these 19 patients underwent successful surgery[1,7,22] and 16 died, all save two from causes directly attributable to the malformation. Two additional patients in the group of 19 studied underwent surgery; in these two infants the vascular ring was not divided and neither of them survived.[13,19,24] The case reported herein appears to be the fourth recorded case in which one component of a double aortic arch has been divided surgically in a

young infant; no doubt other operations of this type have been performed in patients in this age group but have not yet been reported in the literature. In addition, Sweet[22] and Potts[24] have each successfully divided the vascular ring in an older child with a double aortic arch. In each instance an excellent postoperative result was achieved.

The procedure to be carried out on operation will vary according to the exact anatomical abnormality encountered.[7,15,23] Edwards[26] has offered certain rules concerning surgical therapy which appear to be generally applicable. Relief is to be obtained by division of the smaller of the two aortic arches, which is usually the anterior one. Since it is superfluous as a blood conveying structure, whether it is atretic or functioning is of little practical significance. The structure to be divided usually is found in that side of the chest in which the ligamentum arteriosus is situated. The ligamentum generally, but not invariably, lies in that hemithorax in which the proximal portion of the descending aorta is located. The position of the first part of the descending aorta can usually be determined with certainty by carefully executed preoperative x-ray stdies, although in young infants with a double arch this is not always possible, as exemplified by the case reported in this paper. Information as to the location of the proximal descending aorta is usually of great importance so that the surgeon may know in advance the most favorable side upon which to perform thoracotomy. Choice of the less advantageous side through which to carry out exploration may necessitate abandonment of the procedure and re-operation through the opposite hemithorax in order to apply corrective surgery.[22] The point of division of the smaller arch will be determined by the precise situation encountered and a decision can be made intelligently only after the anomaly present has been adequately visualized and is clearly understood. The point chosen may be proximal to the common carotid,[22] between the common carotid and the subclavian[1,7] or distal to the subclavian.[24] The ligamentum or ductus arteriosus should also be divided when it is accessible, thus allowing the pulmonary artery to retract downward and forward and the arch to slide upward and laterally from its point of compression of the trachea. However, based on anatomical grounds and on the meagre surgical experience reported thus far, the latter procedure alone would seem inadequate to sufficiently relieve the pressure on the trachea and esophagus. The vascular ring must be broken at some point before a good result can be reasonably anticipated.[1,7,22,24] The method of closure of the ends of the divided arch will be dictated by the calibre of the structure concerned. An atretic vessel or one of small diameter will require only simple ligation. Where the

severed arterial trunk is patent and of large calibre, closure by suture using a technique similar to that employed by Gross[30] in the management of patent ductus arteriosus would appear to be based on sounder surgical principles. Potts[24] utilized this method in his successful case.

In the uncomplicated case the postoperative care of infants undergoing surgery for a constricting vascular ring should be a fairly simple matter. However, it will doubtless prove true that a large percentage of these babies will be in rather miserable condition before operation is undertaken. Malnutrition will have lowered the patient's resistance and pulmonary infection will be incipient if not well-established. Where this situation prevails attention to the details of pre and postoperative care become all-important. It calls for the closest cooperation between the thoracic surgeon and the pediatrician and the employment of every indicated facility at one's command if these infants are to survive. Their condition can change with dramatic suddeness and unremitting care 24 hours a day is necessary.

Addendum

Since this paper was prepared, Kirklin and Clagett have published (Kirklin, J. W. and Clagett, O. T.: "Vascular 'Rings' Producing Respiratory Obstruction in Infants," Proc. of the Staff Meetings of the Mayo Clinic, 25:360, 367, June 21, 1950) a complete classification of anomalies of the aortic arch, including both observed and hypothetical forms. It is a modification and elaboration of the classification proposed by Edwards.[26] The case reported above would be classed as IIA1a in Kirklin and Clagett's classification. This variety of anomaly is illustrated in their figure 1b, d, page 361. The authors report a case of double aortic arch with left descending aorta and left ligamentum arteriosum. The posterior right arch was the larger of the two. The anterior arch was divided just to the left of the origin of the left subclavian artery and the ligamentum was severed. The left pulmonary artery was mobilized, allowing it to fall forward away from the trachea. Sixteen months postoperative the patient had marked symptomatic relief from the very severe wheezing and coughing which had been her presenting symptoms but she still had some mild wheezing and noisy respirations on occasions. The imperfect operative result was attributed to softening of the tracheal rings due to prolonged pressure and consequent tendency of the trachea to collapse (the patient was three years and eight months of age at the time of operation). This diagnosis was substantiated by bronchoscopic observations. That long maintained pressure on the trachea can cause softening of the cartilages is a well-established

fact and this hazard provides another reason why early surgical interference is indicated in infants with tight vascular rings causing significant symptoms.

Although that possibility must certainly be considered, the clinical course, bronchoscopic observations, and postmortem findings tend to eliminate softening of the cartilages as the cause of the postoperative difficulties in our case.

SUMMARY

1) Certain factors pertaining to double aortic arch have been mentioned.

2) A case presenting a rare type of double aortic arch, previously unrecorded, has been reported.

3) The presence of a congenital vascular ring should be suspected in infants who suffer with stridor, dysphagia and associated symptoms.

4) Those patients with severe symptoms due to a constricting vascular ring will probably not survive if untreated. Surgery offers the only prospect of a cure. It has been demonstrated that young infants possess the ability to withstand major intrathoracic operative procedures surprisingly well. Operation should therefore be performed in these cases promptly after the diagnosis is established.

RESUMEN

1) Se mencionan ciertos factores pertinentes en relación con el doble arco aórtico.

2) Un caso que representa un tipo raro de doble arco aórtico se describe.

3) La presencia de un anillo vascular congénito debe sospecharse en niños que sufren de estridor, disfagia y síntomas asociados.

4) Los enfermos con síntomas severos debido a un anillo vascular constrictor, probablemente no sobreviven si no se tratan. La cirugía ofrece la única posibilidad de curación. Se ha demonstrado que los infantes poseen una capacidad de soportar las operaciones mayores con sorprendente facilidad. El tratamiento debe emprenderse por tanto tan pronto como el diagnóstico se establezca.

RESUME

1) Les auteurs exposent certains éléments propres à l'existence d'un double arc aortique.

2) Ils rapportent un cas où existe une modalité rare de double arc aortique qui, jusqu'à présent, n'avait pas été mentionnée.

3) L'existence d'un anneau vasculaire congénital doit être sus-

pecté chez les enfants qui sont atteints de stridor, de dysphagie, et de symptômes associés.

4) Ces malades atteints de symptômes sévères dus à la constriction par l'anneau vasculaire n'ont probablement aucune chance de survie s'ils ne sont pas traités. La seule possibilité de traitement est chirurgicale. Il est démontré que les tous jeunes enfants sont capables de résister d'une façon surprenante aux interventions intra-thoraciques les plus importantes. C'est pourquoi, dans de tels cas, l'opération devrait être réalisée dès que le diagnostic a été précisé.

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Acute Pulmonary Oedema, Endogenous and Exogenous Causes, with Therapy*

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Sometime in the clinical practice of everyone of us we are faced with the following picture: Usually in the middle of the night when we receive a call so brief and so panic stricken, we sense at once that it is no whimpering neurotic that needs aid. We arrive at the patient's home in record time. Coming up the last few stairs, even before we see the patient, we hear the desperate gasping cough, the choking rattle. We then already know with what we have to deal. We know that in the next few minutes our work will count, only if we have thought out in advance exactly what should be done. Though many terminal heart cases will die regardless of what we do, some can be carried through the emergency and it is worth trying. Hamman states that one case was reported as having 72 seizures of pulmonary oedema occurring over a period of three years.[1]

We know just what the patient will look like. Propped bolt-upright, cyanotic and yet pale, he has collapsed and already there is welling out of his mouth, that tell-tale frothy pink sputum. He has no strength to give answers and we have no time to ask him questions. The patient is drowning before our eyes. He has acute pulmonary oedema. As Conheim puts it in more restrained fashion when speaking of the far advanced cardiac type, he said, "It is well to remember that in a terminal stage of heart disease the patient does not die of pulmonary oedema, but he has pulmonary oedema because he is dying."

In this paper I am not speaking primarily of chronic congestive heart failure but I am concerned chiefly with pulmonary oedema of the acute massive type when the lungs are suddenly flooded with serous fluids. It is a condition that may come on suddenly without warning in a patient outwardly looking quite well. It may be precipitated with the slightest of provocation whether excitement or exertion. On the other hand its onset may almost be predicted if certain therapeutic techniques are carried through carelessly as when the circulation is over-loaded by too rapid and too massive saline intravenous therapy, or when a thoracentesis is performed too rapidly or too thoroughly.

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Nearly 200 years ago in 1752, Moloet, according to Luisada, gave the first recorded clinical report on pulmonary oedema. Since that time hundreds of articles have been written on the cause and treatment of this common yet dramatic clinical syndrome.

Etiological theories for pulmonary oedema whether acute or chronic are largely threefold. One of the earliest and most thorough-going experimental approaches to the problem was contributed in 1878 by Welch. He with his mechanical theory, Luisada with his neurogenic theory, and Drinker with his anoxia theory stand for three schools of thought.

Welch, with his mechanical theory based on a large series of experiments done in his graduate student days in Germany, believed that he had proved the cause of pulmonary oedema. As he recapitulated his original article of 1878 in 1904, he said, "The cause of pulmonary oedema is due to a disproportion between the working power of the left ventricle and of the right ventricle, of such character that the resistance remaining the same, the left heart is unable to expel in a unit of time the same quantity of blood as the right heart."[2]

Based on this experimental cornerstone, for many years nearly all clinicians have considered that acute pulmonary oedema was usually the expression of failure of the left ventricle with resultant symptoms due to back pressure in the pulmonary blood vessels. This seems clinically proved by the frequent occurrence of pulmonary oedema in aortic insufficiency, hypertension, mitral regurgitation, and coronary artery disease where left ventricular failure occurs most frequently.

Paul White, with others, points out that pulmonary oedema is due to left ventricular failure, not right ventricular failure. He recalls that when right ventricular failure with liver enlargement and peripheral oedema follows left ventricular failure, the lung oedema often decreases and may completely disappear.[3]

In the last quarter of a century, however, many European and American authors have reported that pulmonary oedema may occur without left ventricular failure. In 1928 Luisada, formerly Professor of Medicine of the University of Ferrara, Italy, published his experimental work showing that he could produce pulmonary oedema by injecting epinephrin intravenously in rabbits. He also showed that narcotics and sedatives as morphine, papaverin and chloretone prevented pulmonary oedema in a significant percentage of treated cases.

Luisada felt that the adrenalin produced hypertension in aorta, carotid, and cephalic vessels, and this in turn activated a reflex arc which determined the sudden increase in the permeability of the pulmonary vessels and consequent pulmonary oedema. In fact

Luisada and a number of others now believe that the "neurogenic" theory rests on a sounder experimental basis than the older "left ventricle failure theory" of pulmonary oedema. It is interesting to note that they do admit, however, Luisada particularly, the paucity of direct evidence favoring a purely "neurogenic" theory. Luisada also admits that the development and course of pulmonary oedema can best be influenced by well known mechanical procedures, as when by venesection and application of tourniquets to extremities we reduce pulmonary stasis and blood volume.[4]

Certainly the "neurogenic" theory advocates have a strong accumulation of indirect evidence when they list many conditions causing pulmonary oedema apart from left ventricular failure. These include, for example, pulmonary oedema occurring with trauma to the skull and chest, surgical shock, poliomyiitis, encephalitis, brain abscess, brain tumor, meningitis, pulmonary infarction, thoracentesis, uremia, and thyroid crisis as the most common instances.

A third basic approach to the pathogenesis of the problem is that of Cecil Drinker.[5] For many years he and his associates have been studying the formation and movement of lymph in the lung together with the evaluation of the pulmonary lymphatics as a means for removing transudates and exudates from the alveoli. He explains pulmonary oedema as the result of leakage of the capillaries of the pulmonary epithelium lining the alveolar units. He believes that this abnormal transudation is a result of two main factors; one, sustained increase in pulmonary capillary pressure; and two, tissue anoxia which increases permeability of the pulmonary capillaries just as anoxia causes leakage of capillaries all over the body.

Drinker also lists three ways in which the free alveolar fluid may be removed; one, by drifting up the alveoli and bronchial tree as a red frothy sputum to be coughed up as proteinized fluid transudate; two, by the fluid's being reabsorbed into the alveolar capillaries as with enzyme action or by artificially produced positive pressure; and third, by being absorbed into the lung lymphatics. Very recent experiments with the "heart-lung" preparation by Paine, et al., suggest that Welch's original mechanical theory was largely correct but that Drinker too was correct in implying that partial obstruction of pulmonary lymph channels might intensify the development and retention of alveolar oedema.[6]

Drinker may be said to be the protagonist of a middle-ground theory acknowledging the reasonableness of the older mechanical, left ventricle strain explanation and part of the so-called "modern neurogenic" theory. He sees also the importance of recognizing a third factor, namely anoxia, whether produced by low oxygen in

the air which itself increases lung capillary permeability or by local damage to the pulmonary epithelium by lung irritants such as phosgene, oxides of nitrogen, and cadmium fume.

Both Drinker, the physiologist, and Barach, long practiced worker on inhalational therapy, agree on certain fundamental physical factors which must be thoroughly appreciated.[7]

These basic factors include recognition of the fact that pulmonary capillary pressure is about 10 mm. of mercury, usually well under the opposing pull of the colloidal osmotic pressure of blood serum of 25 to 30 mm. This might seem to be a large factor of safety for holding the fluid in the capillaries because the osmotic pressure would seem to pull back fluid by an advantage of 15 to 20 mm. over the capillary pressure. However, this margin of safety may be markedly reduced by the outward suction pull through the capillaries of a negative pressure of 5 to 10 mm. due to normal inspiration. Further, this negative pressure may be increased to as much as 70 mm. of mercury pressure merely by suction of forced inspiration seen for instance in severe exertion, asthma, and partial bronchial obstruction.

This negative pressure pull can be dangerously enhanced by suction pull of mechanical "pulmotor" resuscitation aimed at increasing pulmonary ventilation in both inspiratory and expiratory phases. The positive pressure devices for increased back pressure in both expiration and inspiration, or in the expiration stage alone, are much less likely to increase this negative pressure pull. In fact, as well as theory, they actually tend to push fluid back into the capillaries by the slight balance of positive pressure.

So far we have been discussing chiefly endogenous causes of pulmonary oedema; namely that produced by increased pulmonary pressure due to mechanical causes in cases of long-standing heart strain, but now I should like to discuss some of the exogenous causes of pulmonary oedema due to irritants, gases and fumes. Because the heart is sound to begin with in these cases, they are much more likely to respond to specific treatment.

Bronchial and pulmonary irritation due to harmful and toxic gases was first most tragically brought to general public attention by the First World War use of chlorine in the German surprise gas attack. Then and subsequently in civilian experience in the paper industry when chlorine escapes and is inhaled briefly it is known that there may be a severe insult to the mucosa of the upper respiratory tract. Chlorine is so water soluble that it affects chiefly the upper respiratory tract and is so irritating that usually there is laryngospasm and thus does not reach the lower deep respiratory tract. However, when chlorine workers are trapped so they are forced to breath it deeply, the alveoli themselves may

be damaged with resultant pulmonary oedema. Then there is also the usually almost irrespirable sulfur dioxide gas which is also highly water soluble affecting primarily the upper respiratory tract but which may penetrate deep into the bronchial tree if a man's escape is blocked by an explosion; for instance, when sulfur is being unloaded from a ship's hold and an explosion causes the sulfur to be ignited, he is trapped below deck and forced to inhale burning sulfur.

Delayed pulmonary oedema coming on after a latent period of six to 12 hours may result from the inhalation of phosgene, methyl bromide, phosphorous compounds, oxides of nitrogen, and cadmium fume, as well as of smoke from a great fire such as the Cocoanut Grove Disaster. Because these compounds do not irritate the upper respiratory tract they are inhaled deeply into the alveoli. In that terrible fire of 1942 before positive pressure therapy equipment was widely available, it was the latent pulmonary oedema that killed so many of the victims 24 to 60 hours after the fire, as described by Aub,[8] not just the body burns. One of the explanations for this pulmonary irritation and resultant oedema was that Freon (dichlorodifluoromethane), a refrigerant gas in the air-conditioning system, was heated so that it produced phosgene which in turn escaped when the pipes were burned through as suggested by Finland.[9]

Interestingly enough a five year follow-up study of 16 patients in the Cocoanut Grove fire showed no residual, according to Pittman.[10]

There have been reported a number of cases of the formation of phosgene as a result of the use of carbon tetrachloride as a fire extinguisher in enclosed spaces, recorded by Barach.[11] When thus heated to a relatively high temperature, the carbon tetrachloride (CCl_4) goes over to $COCl_2$ or phosgene which then combines with the moisture in the alveoli to form concentrated hydrochloric acid in the alveoli. The resultant burn causes an oedema reaching its peak after a period of six or eight hours and actually drowning the patient if not treated. It is generally known also that phosgene may be one of the by-products in the atomic energy process. I know from a personal communication of a physician in that work, that when breakdowns in such a phosgene line occurred, workers who had pulmonary oedema had it rapidly relieved by positive pressure oxygen inhalation.

Not too infrequently when welding is done in enclosed spaces even on clean steel or in cases of cutting with an oxyacetylene torch in the repair or scrapping of steel ships, the cutters or burners will not only complain of lead colic symptoms, if the cutting is done on lead painted steel, but also after several hours

these burners may have a delayed development of a tight feeling in the chest sometimes to the point of acute pulmonary oedema. This was proved experimentally by Titus, Warren and Philip Drinker.[12] When recognized in time and the condition is thought of by the physician, it is usually found that these patients are rapidly relieved by oxygen under positive pressure.

There have also been reports of other cases of delayed pulmonary oedema occurring when cadmium plated parts are carelessly welded or smelted after scrapping or when cadmium is ignited accidentally by a fire in a shop handling cadmium as noted by Fairhall.[13] In such cases the workers and firemen involved often have no knowledge that the smoke they are working in contains the deadly fumes of cadmium. Just such an accident was described by Shiels and Robertson of England.[14] A small box of cadmium metal parts was ignited by the fire on a near-by work bench. After several hours, one of the firemen died of acute pulmonary oedema and postmortem examination showed quantities of cadmium in the lungs as well as in the urine.

Fuming nitric acid has the same affect on the alveoli as cadmium fumes. When glass containers of nitric acid are broken accidentally as in a fire, they cause great quantities of oxides of nitrogen fumes to be emitted and endanger the workers and firemen. Some years ago such an accident occurred in Milwaukee with fatal results to several firemen.

Also when workers in plating departments, commonly attached to nearly every modern industry, are "bright-dipping" brass parts in jars of nitric acid, they may be exposed to black or brown nitrogen oxide fumes which cause the same treacherous pulmonary oedema. Elkins gives the maximum allowable concentration for nitrogen dioxide and nitrogen tetraoxide as 10 ppm.[51]

All these cases of alveolar damage due to the inhalation of acid gases or irritating fumes are best treated by oxygen under pressure, either by an intermittent positive pressure instrument as the "Pneophore" or the Barach oxygen mask metered for positive pressure.[16] With the latter mask obstruction of expiration is gradually increased by turning a disc on the mask so that smaller and smaller openings are allowed for expiration. These are calibrated to give the equivalent of one to six cm. of water, positive back-pressure on expiration. The pulmonary oedema usually improves in one to three hours treatment.

Barach recommends beginning the positive-expiration pressure at one or two cm. water pressure increasing gradually up to five or six cm. depending on the cooperation of the patient. Occasionally he does this intermittently. If the pulmonary oedema disappears during the application of a positive pressure of three to six

cm. in a period of several hours, the pressure is lowered to two cm. for one to two hours more. At the end of this time it should be lowered to one cm. for one or two hours more and then removed. In other cases, if pulmonary oedema has cleared, trial of breathing without the mask should be made for a period from five to 30 minutes and if coughing and oedema do not supervene, treatment should be discontinued. If they do occur, the mask should be reapplied with positive pressure.

It is noteworthy here that Barach comments, "When pressure is applied during the expiratory cycle alone there is less apt to be any noteworthy interference with the return of blood to the right side of the heart. This blood may enter the heart during the inspiratory cycle in which negative intra-pulmonary pressure naturally facilitates the iniet of blood into the right auricle." Therefore inspiration must not be under positive pressure but only in expiration and that cautiously in surgical shock and emphysema.

Carlisle also reports an excellent result from administration of oxygen under atmospheric pressure with provision for expiration against calibrated resistance of from one to six cm. of water pressure. He notes his experience with its successful use in 316 cases of pulmonary oedema from chemical inhalation with no fatality in a period of nine years. He advises also the administration of 1 to 100 solution of epinephrin by the oral nebulizer method.[17]

From the point of view of treatment one should take into consideration all three etiological theories, mechanical, neurogenic and anoxia. Pulmonary oedema found to be due to the transudation of proteinized fluid caused by mechanical or neurogenic factors we may call endogenous and we may consider the exudate of inflammatory fluid due to infection or irritation simply as exogenous pulmonary oedema.

Whatever the cause and whatever the theories, the therapy of such conditions is improved and made more effective by the immediate application of several simple procedures. First, to reduce pulmonary stasis and blood volume one should try the serial application of extremity tourniquets and possibly venesection. This reduces the right ventricle inflow and its preponderance over a failing left ventricle as emphasized by the mechanical theory proponents.

Second, the application of certain narcotic and sedative drugs such as morphine and papaverin as well as chloretone and phenobarbital is of value as suggested by the "neurogenic" theory.

Third, one should use oxygen under slight positive pressure to buttress the leaking pulmonary capillaries. This last and newest form of therapy is the contribution from the experience of the

physiologist and specialist trained to meet inhalational emergencies in industry and war, whether dealing with carbon monoxide, cadmium fume, oxides of nitrogen, or phosgene intoxication.

Actually in clinical practice at the earliest suspicion of the need of oxygen in a case of pulmonary oedema occurring in the home, it is well to put in a call for the fire department rescue squad. They can be counted upon to put in their appearance with an oxygen inhalator in from eight to 10 minutes, before the commercial suppliers of oxygen can possibly arrive. The equipment usually used by the firemen is not a pulmotor but is an actual oxygen inhalator which operates under a slight, though not calibrated positive pressure and uses usually 95 per cent oxygen with five per cent carbon dioxide. No harm and much good is done by this equipment which can be safely used an hour or so until the positive-pressure equipment using 100 per cent oxygen is delivered to the home. Luisada has shown that certain anti-foaming agents, notably ethyl alcohol, when administered by inhalation have remarkably improved the survival time and reduced the severity of pulmonary oedema experimentally induced in animals.[18]

Clinical studies using this alcohol therapy were reported by Luisada at the American Heart Association in June 1951.

Surely a physician, or better still a medical team, trained to utilize all of these procedures is most likely to prolong life. With our ever increasing concern for preparedness against great fires in war target-areas involving heavy chemical industries, every physician must not only be familiar with oxygen equipment for positive-pressure inhalation but he must learn to be alert for the unpredictable pulmonary oedema in patients. This may suddenly appear after a latent period of a day or so following the inhalation of smoke and fumes.

If we have been attending the patient as a known hypertension or heart case probably such a case as I described at the opening of this paper is likely to be simply an acute heart failure, an instance of endogenous pulmonary oedema. If, however, we are called to the bedside of someone we have not known previously, after applying the above mentioned accepted emergency measures, it is our responsibility to get an accurate history of occupational exposure from any member of the family able to give it. It is possible that we may be dealing with an instance of exogenous pulmonary oedema.

We should recall, then, in any such emergency, that this type of pulmonary oedema may occur after a latent period of several hours whether caused by exposure to cadmium fumes from welding or smelting, from oxides of nitrogen fumes either from welding in enclosed spaces or from "bright-dipping" of plating parts in nitric

acid, or from spillage of a large amount of nitric acid. Johnstone reports specific cases where the physicians missed the etiological diagnosis because they did not think to inquire regarding the occupation.[19]

We should bear in mind also that when a householder or a fireman uses carbon tetrachloride or other chlorinated solvents under conditions where they are exposed to high heat, that the phosgene vapor may be generated and thus cause a fatal pulmonary oedema.

Our acuteness in differentiating between endogenous and exogenous pulmonary oedema is demanded finally by the question on the possible death certificate, "Is this case occupationally connected?" If we cannot save the patient by well chosen therapy we are certainly bound to help the family, and perhaps later even the Court, to understand the distinction, medical and legal, between endogenous and exogenous pulmonary oedema.

SUMMARY

This paper is concerned with acute pulmonary oedema of the massive type. We define pulmonary oedema due to transudation of proteinized fluid caused by mechanical or neurogenic factors as endogenous, and that due to exudate of inflammatory fluid due to infection or irritation as exogenous.

Regarding treatment, we must consider all theories of etiology. First, to reduce pulmonary stasis and blood volume we should apply serially extremity tourniquets and possibly venesection as approved by the proponents of the "mechanical" theory.

Second, we should consider application of certain narcotic and sedative drugs like morphine and papaverin as well as chloretone and phenobarbital as suggested by the "neurogenic" theory.

Third, we should use oxygen under positive pressure to buttress leaking pulmonary capillaries according to the exponents of the "anoxia" theory. This last and newest form of therapy is the contribution from experienced physiologists and specialists trained to meet inhalational emergencies in industry and war, those due to carbon monoxide, cadmium fume, oxides of nitrogen, or phosgene intoxication.

With our need for preparedness against great fires in war target-areas involving heavy chemical industries, every physician must be familiar with oxygen equipment for positive-pressure inhalation. He must be alert for the unpredictable pulmonary oedema coming on after a latent period of several hours, following the inhalation of smoke and fumes.

While many cases of acute pulmonary oedema are those seen in terminal states of hypertensive heart disease, an instance of endogenous oedema, it is our responsibility to get an accurate history

of occupational exposure at once because we may be dealing with an instance of exogenous pulmonary oedema due to inhalation of a pulmonary irritant which, if recognized early, may well respond to oxygen treatment under pressure.

RESUMEN

Se trata de la aguda edema pulmonar y abultada. Consideramos endógena la edema pulmonar que se cause por el trasudor de un fluido proteinizado de origen mecánico o neurogénico, y exógena la que resulta del exudar un fluido inflamatorio debido a la infección o a la irritación.

En cuanto al tratamiento debemos considerar todas las teorías de la etiología.

Primero, para reducir la estancación y el volumen de la sangre en los pulmones hay que servirse de torniquetes sucesivos en las extremidades y tal vez de la flebotomía aprobada por los proponentes de la teoría "mecánica."

Segundo, debemos considerar la aplicación de unas drogas narcóticas y sedativas, tales como morfina, papaverin, chloretone y fenobarbital, acción que se sugiere por la teoría "neurogénica."

Tercero, debemos usar el oxígeno bajo una presión positiva para fortalecer los vasos capilares rotos de los pulmones según los exponentes de la teoría "anoxia." Es este nuevo método de la terapéutica la contribución de fisiólogos peritos y de especialistas hábiles en los aprietos de inhalación, aprietos en la industria tanto como en la guerra, debidos al monóxido de carbono, vapores de cadmio, óxidos de nitrógeno o evenenamiento fosgénico.

Siendo preciso prepararnos contra el incendio en los barrios de industrias químicas, especialmente en caso de la guerra, cada médico debe ser versado sobre el equipo con oxígeno para la inhalación de presión positiva. Debe estar alerta para notar la edema pulmonar que no puede pronosticarse y que se hace notar después de estar latente unas horas después de la inhalación de humo y de vapores.

Aunque muchos casos de aguda edema pulmonar se hallan en condiciones terminales de enfermedades del corazón hipertensivo, ejemplo de edema endógena, tenemos la obligación de investigar inmediatamente la situación ocupacional porque puede tratarse de una manifestación de edema oxógena debida a la inhalación de un irritante pulmonar, la cual puede ajustarse bien al tratamiento de oxígeno bajo la presión.

RESUME

Cet article se concerne avec l'oedème pulmonaire aigü du type massif. Nous définissons comme endogène, l'oedème pulmonaire dû

à la transsudation de fluide protéinisé, causé par des facteurs mécaniques ou neurogénics, et comme exogène, celui dû à l'exsudat de fluide inflammatoire causé par infection ou irritation.

Quant au traitement, il faut considérer toutes les théories d'étiologie. D'abord, our réduire la stase pulmonaire et le volume du sang, nous devons appliquer, par séries, des tourniquets aux extrémités, et peut-être la phlébotomie, un procédé approuvé par ceux qui favorisent la théorie "mécanique."

Deuxièmement, nous devons considérer l'application de certains narcotics et de drogues sédatives, comme la morphine et le papaverin, aussi bien que le chlorotone et le phénobarbital, comme le propose la théorie neurogénique.

Troisièment, nous devrions nous servir d'oxygène sous pression positive pour arrêter l'écoulement pulmonaire capillaire, selon les représentants de la théorie "anoxia." Cette dernière et plus récente forme de thérapie vient des physiologistes et spécialistes préparés à traiter, dans l'industrie et la guerre, des cas urgents dûs à l'inhalation du carbone sous-oxyde, de l'exhalaison du cadmium, des oxydes d'azote, ou à l'intoxication causée par les exhalaisons phosgène.

A cause de notre besoin d'être préparé contre des incendies dans les localités menacées par la guerre, où il y aurait d'importantes industries chimiques, chaque médecin doit se familiariser avec l'équipment d'oxygène pour les inhalations sous pression positive. Il doit se tenir sur ses gardes en cas d'oedème pulmonaire inattendu qui pourrait se déclarer après une période latente de plusieurs heures après l'inhalation de fumée et de gaz.

Tandis que beaucoup de cas d'oedème pulmonaire aigü sont ceux que l'on voit à l'etat final des maladies de coeur du type hypertension, un cas d'oedème endogène, il est aussi de notre responsabilité d'avoir tout de suite un rapport complet de la situation industrielle de la personne exposée. Ce rapport doit être fait immédiatement parce que l'on peut avoir affaire avec un cas d'oedème exogénic dû à l'inhalation d'un irritant pulmonaire, qui, s'il est reconnu de bonne heure, pourrait bien répondre au traitement d'oxygène sous pression.

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Pneumonectomy in the Treatment of Tuberculosis in Children*

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Pulmonary resection in tuberculous adults is universally accepted by thoracic surgeons in cases of thoracoplasty failure, tuberculous bronchiectasis, pneumothorax failure, destroyed lung, lower lobe cavity, giant cavity of upper lobe, bronchostenosis and tuberculoma.

Jones and Howard (Diseases of the Chest, December 1949) made reference to resection in two children, one of whom was seven years old. The indications were similar to those for which we have done pneumonectomy, such as pulmonary retraction with atelectasis and pneumonitis with secondary bronchiectasis.

The present paper deals with four resections performed at the Sanatório do Mandaquí, State of Sao Paulo, Brazil. The patients were two white and two Negro girls, varying from 8 to 13 years old.

In each of them the disease was on the left side with the clinical picture described by M. Tapia as "tísica cirrótico-atelectásica." In each case as seen from planigrams and anatomic-pathological specimens, total atelectasis was found with patent main and lobar bronchi. Atelectasis was due to obstruction of peripheral bronchi with chronic pneumonitis, secondary bronchiectasis and active tuberculosis.

Since the indication for pulmonary resection in children is not yet clearly established, and there was need for a carefully controlled experience it was decided to use this method in a few cases. At the outset it should be understood that it is only after the expiration of several years that the end results of treatment in such a few cases will be known.

It has been encouraging to observe with what frequency these young patients have made uncomplicated, smooth and early recovery during the immediate postoperative period with excellent healing.

General Management of the Cases

Only the last and oldest patient was given streptomycin (15.0

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grams) before and after surgery with a dosage of one half gram daily and 1,476 grams of para-aminosalicylic acid.

We used penicillin in the pleural cavity, locally around the stumps of the bronchi and also as prophylactic chemotherapeutic agent with the intention of minimizing the development of secondary pyogenic infections.

Cyclopropane, ether and oxygen anesthesia administered intratracheally was used. All but one patient was placed in the prone position as recommended by Overholt. The incision was carried out postero-laterally, with resection of the full length of the fifth or the sixth rib and small para-vertebral segments of the ribs situated above and below.

We did not cover the bronchus stump with pleura because we divided it as high as possible, near the carina in order to permit the end of the bronchus to retract deep into the mediastinum and thus be covered with the loose, areolar, connective tissue of these surrounding structures.

The sutures were placed in the bronchus in such a fashion as not to interfere with the blood supply of the stump, i.e., three or four terminal cotton stitches are sufficient.

The hilar structures were individually ligated. Resection of the phrenic nerve was done. In the closure of the chest wall the ribs were approximated with three pericostal cotton sutures and the intercostal muscles were sewed with a continuous fine cotton suture. The same was done with the thoracic muscles and skin. Drainage was not used.

Case Reports

Case 1: C.A. is a nine year old white girl in contact with a contagious case of tuberculosis in the family. Diagnosis: far advanced pulmonary tuberculosis with cavitation in the left lung. "Tísica cirrótico-atelectásica" (Figure 1 and 2). Duration of disease was two years. She had positive and negative gastric washings.

On clinical examination we elicited moist stertors of medium and large sizes throughout the left hemithorax with dullness to percussion. The hemosedimentation rate was 43 mms., at the end of one hour (Westergreen) on August 6, 1949.

Pneumonectomy was done on August 8, 1949 with patient in right side position, under intra-tracheal with cyclopropane ether and oxygen anaesthesia. The sixth rib and small para-vertebral segments of fifth and seventh ribs were resected. The extra-pleural separation was arduous and gangli at the hilum rendered dissection difficult. The elements of the pulmonary pedicle were individually ligated beginning with the bronchus (Figure 4). Duration of the intervention was two hours and 15 minutes. Blood transfusion 1,000 cc. The postoperative period was without incidents. Frequent observation has revealed the patient in excellent condition (Figure 3). She is attending school regularly.

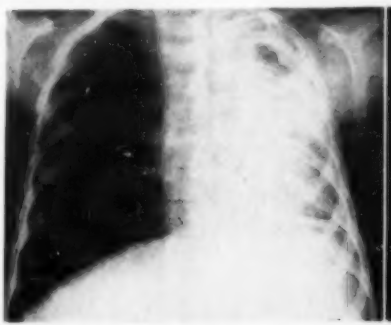

FIGURE 1

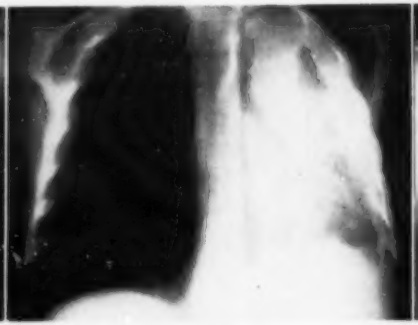

FIGURE 2

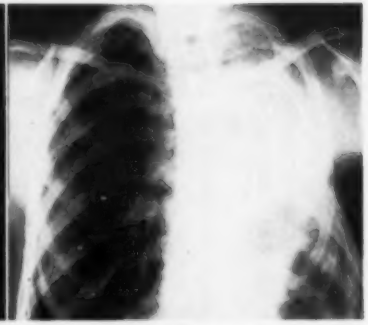

FIGURE 3

Figure 1, Case 1: X-ray film inspection revealed opacity of the left hemithorax, with accentuated shift of the mediastinum to the left, rise of the diaphragm, costal retraction with an area of rarefaction at the level of the third posterior interspace.—*Figure 2, Case 1:* Planigraphy shows the opacity of the hemithorax, the shift of the trachea, patent main bronchus and rarefaction zone in the upper third.—*Figure 3, Case 1:* Last x-ray inspection on July 24, 1950, almost one year after the intervention. Negative gastric washing, hemosedimentation rate 3 mms. at end of one hour (Westergreen).

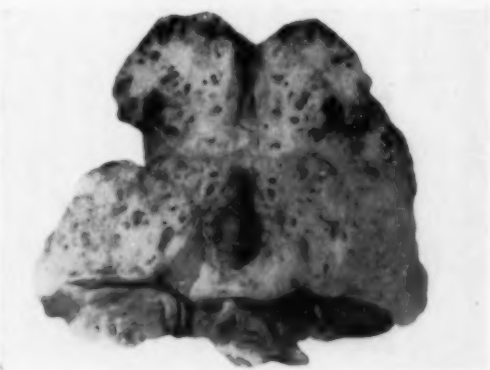

Figure 4, Case 1: Anatomic-Pathological specimen.

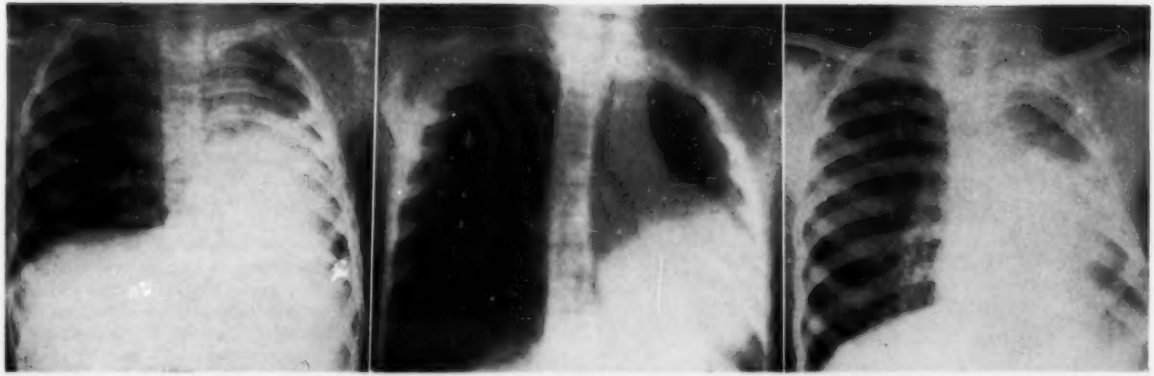

FIGURE 5 FIGURE 6 FIGURE 7

Figure 5, Case 2: X-ray film reveals opacity of the left hemithorax, with accentuated shift of the mediastinum to the left. Note rise of diaphragm and retraction of ribs. Clear zone in the upper lateral third, which in lateral view shows anterior mediastinal hernia of the right lung.—*Figure 6, Case 2:* Planigram shows retraction of the left lung applied against the vertebral column; patient main bronchus and aerated zone in the upper third.—*Figure 7, Case 2:* From x-ray film made May 25, 1950. Patient in excellent condition. Negative gastric washing. Hemosedimentation rate 6 mms. at end of one hour (Westergreen).

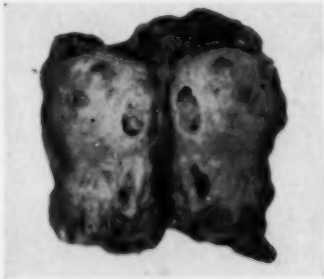

Figure 8, Case 2:
Anatomic-Pathological specimen.

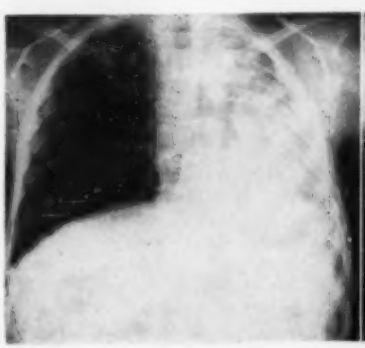

FIGURE 9

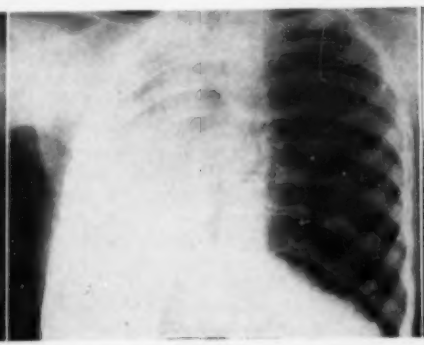

FIGURE 10

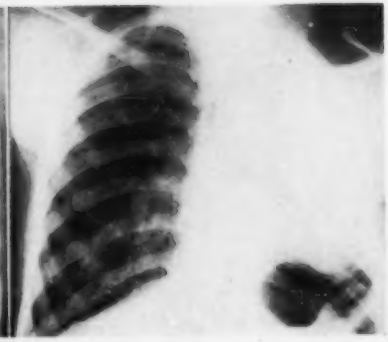

FIGURE 11

Figure 9, Case 3: From x-ray film made on September 2, 1946. Shows opacity of the left hemithorax, with accentuated shift of the mediastinum, costal retraction, patent main bronchus and aerated zone in the upper third.—*Figure 10, Case 3:* X-ray film made on May 13, 1949 (inverted copy). Shows great accentuation of the shift of the mediastinum, opacity of the left hemithorax, rise of the diaphragm, costal retraction and small calcified nodules on right side.—*Figure 11, Case 3:* From x-ray film made on July 10, 1950. Negative gastric washing. Hemosedimentation rate 1 mm. at end of one hour. Patient in excellent condition.

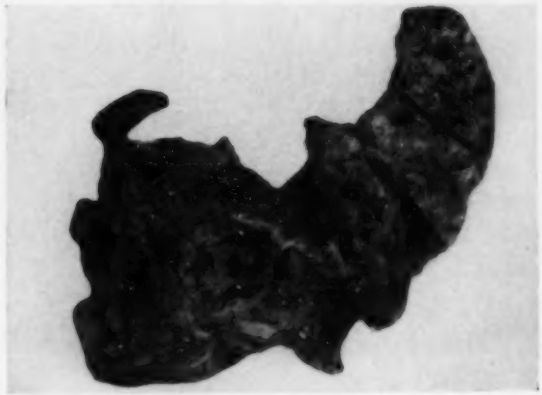

Figure 12, Case 3: Anatomic-Pathological specimen.

FIGURE 13

FIGURE 14

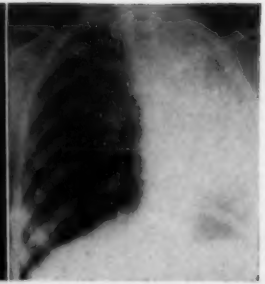

FIGURE 15

Figure 13, Case 4: From x-ray film taken on January 26, 1950. Accentuation of mediastinal shift to left. Opacity of left hemithorax and small calcified nodules in the right lung.—*Figure 14, Case 4:* Planigram made on May 21, 1950. Shows shift of mediastinum to the left, atelectasis of the upper third of left lung and cavitation in middle third.—*Figure 15, Case 4:* From an x-ray film of the chest taken on July 27, 1950.

Figure 16, Case 4: Anatomic-Pathological specimen.

Since secretion was still present in spite of the preoperative care and the anesthetist had to do bronchial aspiration a few times with difficulty before the ligation of the bronchus, we adopted the face down position in the other cases.

Case 2: N.B.D. is a Negro girl, eight years old, with exposure to contagious tuberculosis. Diagnosis: far advanced pulmonary tuberculosis. "Tisica cirrótico-atelectásica" of the left lung (Figures 5 and 6). Duration of disease, three years. On clinical examination, numerous moist stertors to large bubbles were elicited in the left hemithorax, more frequent in the upper third, with dullness to percussion. Positive and negative gastric washings were reported. The hemosedimentation rate was 56 mms. at the end of one hour (Westergreen).

Pneumonectomy was done on September 2, 1949 with patient in face down position, under cyclo-ether-oxygen intra-tracheal anesthesia. The fifth and small segments of the fourth and sixth ribs were resected. The lung was entirely and firmly adherent to the costal wall and the costo-vertebral gutter. Hernia of right lung was found occupying part of left hemithorax. No gangli in the lung pedicle. The bronchus was first ligated with terminal cotton stitches. Duration of the operation was one hour and 55 minutes (Figure 8). Blood transfusion 800 cc. During surgery only a few aspirations of sputum were done. Recovery was prompt and she returned to her usual activities (Figure 7).

Case 3: M.A.P. is a nine year old Negro girl, exposed to contagious case of tuberculosis. Diagnosis: far advanced pulmonary tuberculosis, left lung with cavity. "Tisica cirrótico-atelectásica" (Figures 9 and 10). Duration of disease was more than three years. Positive and negative gastric washing. Hemosedimentation rate was 6 mms. at end of one hour (Westergreen). Moist stertors elicited over left side of chest.

Pneumonectomy was performed on February 27, 1950 in face down position under intra-tracheal anesthesia with cyclo-ether-oxygen. The fifth rib and small para-vertebral segments of the fourth and sixth ribs were resected. The lung was removed and the operation required one hour and 40 minutes (Figure 12). The postoperative period was without incident (Figure 11).

Case 4: M.R.G. is a 13 year old white girl with a contagious case of tuberculosis in the family. Diagnosis: far advanced pulmonary tuberculosis with cavity in the left lung. "Tisica cirrótico-atelectásica." Atelectasis due to obstruction of the peripheral bronchi (Figures 13 and 14). Duration of disease was 18 months. Tubercle bacilli in gastric washings. Hemosedimentation rate, 15 mms. at the end of one hour (Westergreen). Preoperatively she was given in usual doses a total of 1,476 grams of para-aminosalicylic acid and 15 grams of streptomycin in doses of one half gram daily.

Pneumonectomy was performed on June 6, 1950 in face down position with intra-tracheal anesthesia with cyclo-ether and oxygen. The sixth rib and small para-vertebral segments of the fifth and seventh sibs were resected. The lower lobe was free of adhesions, but the upper lobe was strongly adherent to the costal wall. The lung was removed in two hours and five minutes (Figure 16). The postoperative period was without incident.

She is still in the sanatorium and is in excellent condition (Figure 15). Negative gastric washing.

Comments

A satisfactory exposure is obtained by the postero-lateral incision with the patient in the prone position by the removal of one rib in the full length and the resection of short para-vertebral segments of the ribs situated above and below. This provides adequate space and permits the exploration of the hilar structures without traumatizing the pulmonary tissue.

The resection of these ribs—without removal of the transverse processes in children—has not yet resulted in scoliosis. The elevation of the diaphragm caused a good reduction of the hemithorax space and prevented overdistention of the contra-lateral lung.

The only single difficulty that we met was the lack of cooperation of children in relation to cough as they were frequently afraid to expectorate due to pain. To obviate this they were turned at least every hour, and pain was relieved by sedation. Nurses were constantly encouraging them to cough and raise bronchial secretions. These young patients were encouraged to get up as soon as possible which they did with greater facility than adults, and recovery was more prompt.

It is necessary to follow larger groups of children treated by partial or total pulmonary resection in order to make a more final appraisal of its value.

SUMMARY

Four cases of pulmonary tuberculosis in children treated by resection are presented. The ages of the patients varied from eight to 13 years. All were girls, two whites and two Negroes.

These cases were of "tisica cirrótico-atelectásica," of the left side and were treated by pneumonectomy. No complication occurred in the postoperative period, and each one experienced early recovery. All gastric washings became negative soon after pneumonectomy and remained so.

RESUMEN

Se presentan cuatro casos de tuberculosis pulmonar en niños, tratada por neumonectomía. Las edades variaron de 8 a 13 años. Todas fueron niñas: dos blancas y dos negras.

Estos cuatro fueron de "tisis cirrótico-atelectásica" del lado izquierdo y fueron tratados con neumonectomía. No hubo complicaciones en el postoperatorio y todas se recuperaron pronto. Todos los lavados gástricos se volvieron negativos después de la operación y así han permanecido.

RESUME

Les auteurs présentent quatre cas de tuberculose pulmonaire chez des enfants qui ont été traités par exérèse. L'âge des malades s'étend de 8 à 13 ans. Il s'agissait de fillettes, deux de race blanche, deux de race noire.

Ces cas de tuberculose étaient du type de tuberculose scléro-atélectasique, du côté gauche, et furent traités par pneumonectomie. Il n'y eut aucune complication post-opératoire, et dans chaque cas la convalescence fut rapide. Très vite après la pneumonectomie, les tubages gastriques devinrent négatifs, et le demeurèrent.

Late Complications of Extrapleural Pneumonolysis with Plombage

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Introductory Statement

Extrapleural pneumonolysis and maintenance of collapse with paraffin, oil or with refills of air is no longer a popular procedure in the United States. This is obvious from the decreasing number of reports in the literature and from the few follow-up reports from most of those who were enthusiastic about the procedure when it was at the height of its popularity a dozen years ago. The English language literature from 1947 to July 1950 contains only six follow-up reports,[1,7,14,28,33,36] one of these originating in Mexico,[1] one in England[28] and one in Canada.[36] In the foreign language literature reports are more numerous. The introduction of lucite as the supposedly ideal filling substance had but a feeble resuscitating effect on the procedure. The scarcity of reports of late results and complications is the principal reason for reporting several instances of late complications, some rather serious, which I had the opportunity to observe or to treat. It is not implied that such complications eventually develop in most patients subjected to extrapleural pneumonolysis with filling, but as a glance at Table I will indicate the mortality and morbidity rates are such that the unpopularity of the procedure is understandable.

Extrapleural Pneumonolysis with Paraffin Filling

Case I: Figure 1 represents the March 1950 roentgenogram of one of John Alexander's early patients who was subjected to a bilateral extrapleural pneumonolysis with paraffin plombage in 1931 and whose case is presented in some detail in Alexander's medical classic, the Collapse Therapy of Pulmonary Tuberculosis.[2] The preoperative films revealed bilateral disease with cavitation; the current roentgenogram shows no change when compared with the 1933 roentgenogram also reproduced in Alexander's book. This patient began expectorating paraffin 18 months postoperatively and has continued to do so off and on to date. When last seen at the Los Angeles City Health Department she reported to the examining physician a very slight hemoptysis in March 1950; this was her only complaint aside from expectoration of paraffin; the tuberculous process appeared to be arrested. It is not known from

which side the paraffin is expectorated but one would suspect the left side because it was more extensively involved and the weight of the filling was more than double that on the right side. As Alexander stated in his book, expectoration of paraffin is compatible with a fairly good clinical status.

TABLE I: MOST COMMON COMPLICATIONS OF EXTRAPLEURAL PNEUMOTHORAX (AND OLEOTHORAX) REPORTED FROM 1940 TO JULY 1950

REPORTED In	By	Number of Patients	Duration of Postopera-tive Follow-up in Years	Mortality* Per cent	Fistula** Per cent	Extra-pleural Empyema† Per cent
1940	Dolley, Jones and Skillen[9]	135	1-1.5	4	1.5	10.4
	Newton, Dawson and Dunphy[20]	21	1.5	5	5	5
1941	Overholt[24]	48	1-2.5	14.5	14.5	27
	Simmonds and Hounslow[31]	44	1-3.5	23	?	22
	Hedberg[15]	20	2	10	10	25
	Benjamin[4]	29	3	7	?	27
1942	Geary[10]	75	3.5	8	6.5	37.3
	Thompson and Janes[37]	30	0.5-3	0	0	40
	O'Brien, Tuttle and Day[22]	38	1	16	5	29
1943	Russo[29]	38	4	10	6	32
1946	Stoyko[35]	150	?	1.4	2	25
	Reid[27]	54	2-6	9	2	27.5
	Alley[3]	48	3-6	8	8	14
	Maier and Hurst[17]	1	1	0	0	0
1948	Alarcon[1]	201	2-8	4.5	1.5	7.3
	Sullivan[36]	82	1.5-8	8.5	6	5
	Roberts[28]	100	1-9	14	7	28
	Head and Moen[14]	86	3-11	3.5	2.3	13
	Smart, Samson and Childress[33]	45	5-9	2+	11	38
	Jones[16]††	47††	9	?	0	20

*Attributable to the operation. **Bronchoextrapleural and extrapleurocutaneous. †Tuberculous, pyogenic and mixed. ††These 47 patients were part of 135 reported in 1940 by Dolley et al.[9] and were operated on between October 1937 and October 1938.

Case II: Figure 2 represents the roentgenogram of a young individual who began expectorating paraffin about six years after extrapleural pneumonolysis with paraffin filling. In this case the pulmonary process was unilateral and limited to the extreme apex. Aside from the expectoration of paraffin there were no complaints and the tuberculous process appeared arrested.

Case III: Figure 3 represents the preoperative roentgenogram of a 47 year old female with a bilateral upper lobe process more extensive on the right where cavitation was present. Following clinical failure of right intrapleural pneumothorax and right phrenic nerve crush, right extrapleural pneumonolysis with wax filling was done in June 1937 and she was discharged in August 1938 as a successful result (Figure 4). She remained well to date except for a chronic and slightly productive cough and expectoration of slivers of wax in 1945 (Figure 5) and passage of wax with stools in 1948 (Figure 6); the wax passed rectally was in the form of marbles 1 to 1.5 cm. in diameter, as described by the examining physician. When last seen at the Los Angeles City Health Department in April 1950 (Figure 7) the patient reported to the examining physician that there was no discharge of wax at the time. The serial roentgenograms reproduced in Figures 5, 6 and 7 demonstrate progressive diminution in the size of the wax filling. In the absence of other signs of esophagoextrapleural fistula and

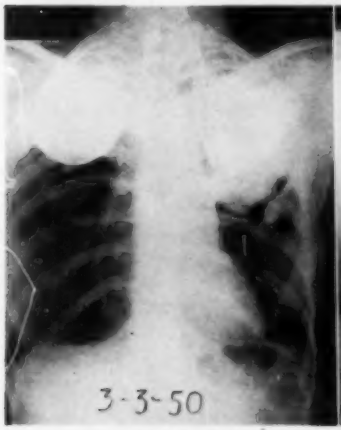

FIGURE 1

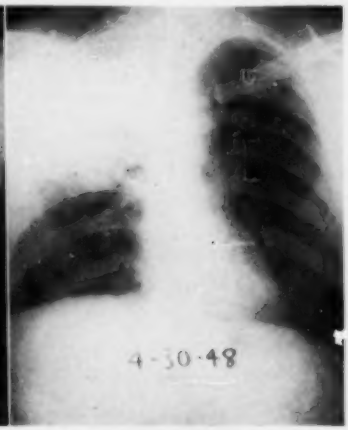

FIGURE 2

Figure 1, Case I: Bilateral extrapleural paraffin plombage in 1931. Intermittent expectoration of slivers of paraffin since 1933. Pulmonary disease inactive.—*Figure 2, Case II:* Unilateral paraffin plombage in 1942. Intermittent expectoration of slivers of paraffin since fall of 1947. Pulmonary disease inactive.

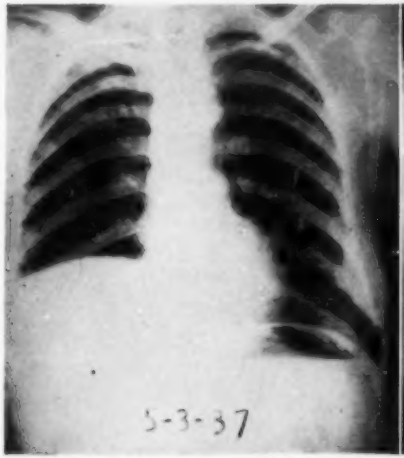

FIGURE 3

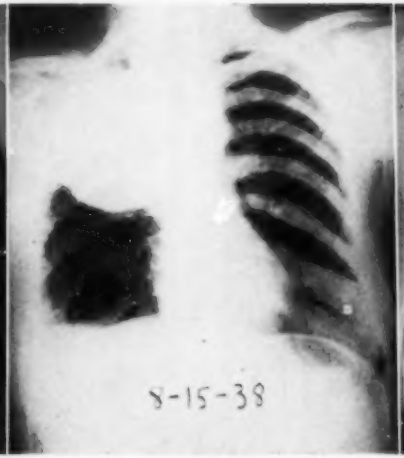

FIGURE 4

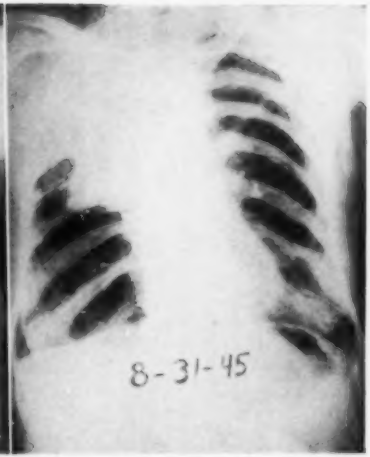

FIGURE 5

Figure 3, Case III: Preoperative chest roentgenogram following right phrenic crush and failure of right intrapleural pneumothorax. Excavation present in upper half of right lung.—*Figure 4, Case III:* Right extrapleural wax plombage in June 1937. Discharged as successful in August 1938.—*Figure 5, Case III:* Expectoration of slivers of wax began in 1945.

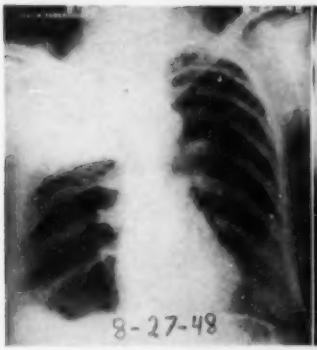

FIGURE 6

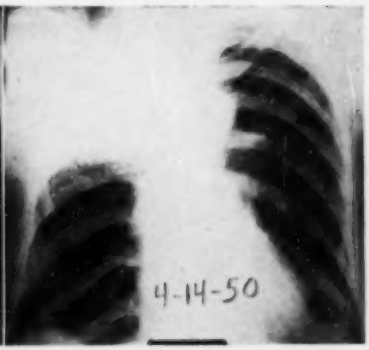

FIGURE 7

Figure 6, Case III: Expectoration of wax continued intermittently with wax in stools. Size of filling is smaller and inferior border of space poorly defined. *Figure 7, Case III:* Further diminution in size of filling. Pulmonary disease remains inactive.

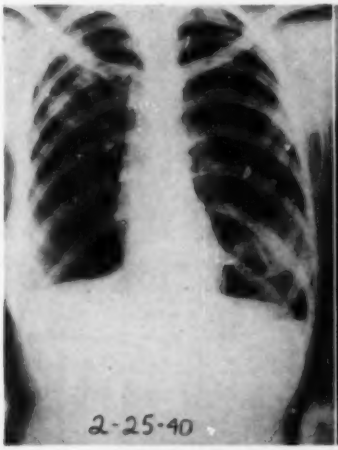

FIGURE 8

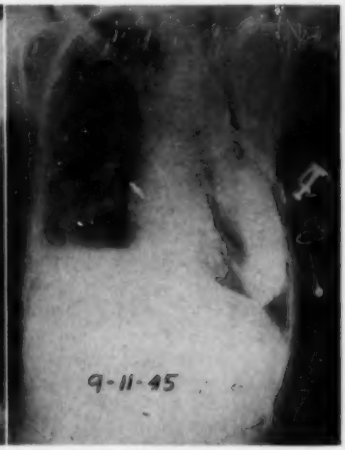

FIGURE 9

Figure 8, Case IV: Chest roentgenogram showing left intrapleural pneumothorax with restricting adhesions but no evidence of activity in the partially collapsed lung; also infiltration and excavation in the upper half of the right lung.—*Figure 9, Case IV:* Left extrapleural pneumothorax in February 1942 followed by empyema and conversion to oleothorax; recurrence of empyema and spontaneous perforation through esophagus with expulsion of contents of space in the form of oily stool in March 1945. Open drainage and thoracoplasty done. Chest roentgenogram represents status in September 1945 shortly after the patient presented herself with esophago-extrapleurocutaneous fistula.

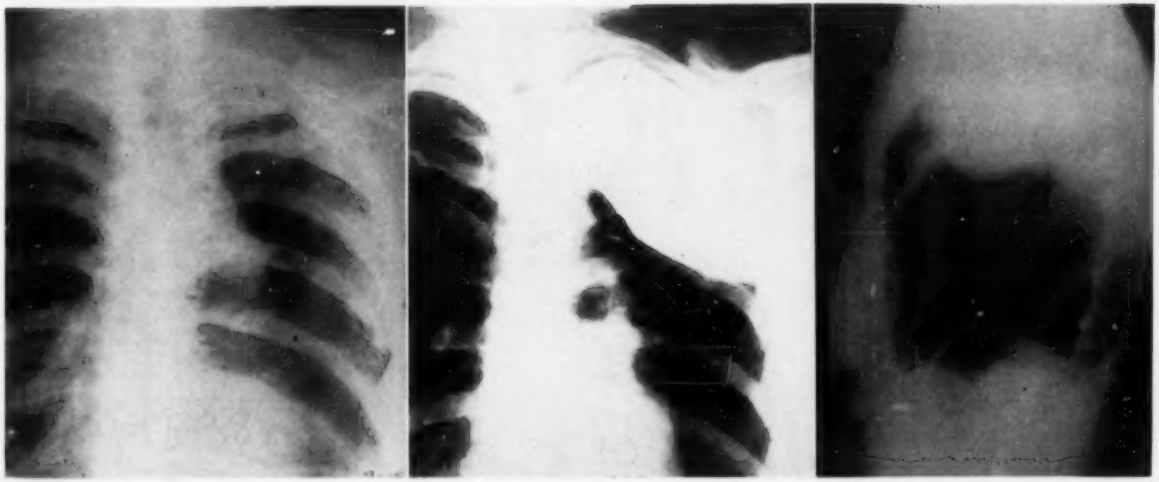

FIGURE 10 FIGURE 11 FIGURE 12

Figure 10, Case V: Preoperative chest roentgenogram showing 1 x 1½ inch cavity in the left upper lobe between 4th and 6th posterior ribs.—*Figure 11, Case V:* Left extrapleural pneumothorax done in October 1938 and converted to oleothorax in September 1939. Roentgenogram shows status in January 1940, at the time of discharge from sanatorium as a successful result.—*Figure 12, Case V:* Left lateral roentgenogram in May 1948, showing posterior bulging of chest wall due to empyema necessitans. Fluid level between pus and oil seen in original roentgenogram.

due to the fact that according to the members of the patient's family she has been suffering from mental confusion, it is probable that the wax was first expectorated, then ingested and passed rectally.

Comment: According to Alexander,[2,18] extrapleural pneumonolysis with paraffin filling was adopted at the University of Michigan Hospital in 1930 because it appeared to offer a collapse procedure to patients in whom intrapleural pneumothorax failed and thoracoplasty was contraindicated. Case I belongs in this category, but cases II and III do not. In subsequent reports by the same workers[19] made on the basis of additional operative experience and postoperative observation it was suggested that inasmuch as results with paraffin plombage in patients suitable for thoracoplasty were extremely satisfactory it depended on circumstances in individual cases whether or not extrapleural pneumonolysis with paraffin filling should be used as a substitute for thoracoplasty. Fifteen years after the adoption of extrapleural pneumonolysis with paraffin filling Steele[34] reported good early results and few complications, but a high percentage of his patients appeared to be entirely suitable for thoracoplasty; he recommended extrapleural pneumonolysis with paraffin filling for patients with apical cavities not larger than 1.5 cm. in diameter. In other words, the indications for this procedure were extended to patients who were good thoracoplasty risks; in such cases this operation was applied as a substitute for thoracoplasty.[19,23,34] In the latest report on this subject made in 1948 and published in 1950[7] it was again maintained that extrapleural pneumonolysis with paraffin filling should not be in competition with any collapse procedure, particularly thoracoplasty, and at the same time it was also stated that the ideal patient for this procedure was the one with a unilateral apical cavity not greater than 2 cm. in diameter and this type of lesion was the first on the list of indications for extrapleural pneumonolysis with paraffin filling. In a series of 186 patients collected from the literature by Decker[7] and most of whom were observed for only up to several years there was a 13 per cent incidence of bronchoextrapleural and bronchoextrapleurocutaneous fistulae. Head[12] suggested the employment of extrapleural pneumonolysis and paraffin filling in patients with large apical cavities not suitable for primary thoracoplasty, but who might improve following pneumonolysis to withstand thoracoplasty.

Extrapleural Pneumothorax and Oleothorax

Extrapleural pneumothorax is within the scope of this report since the operative procedure is one of pneumonolysis, i.e., freeing the lung from the chest wall, because air is a form of filling and

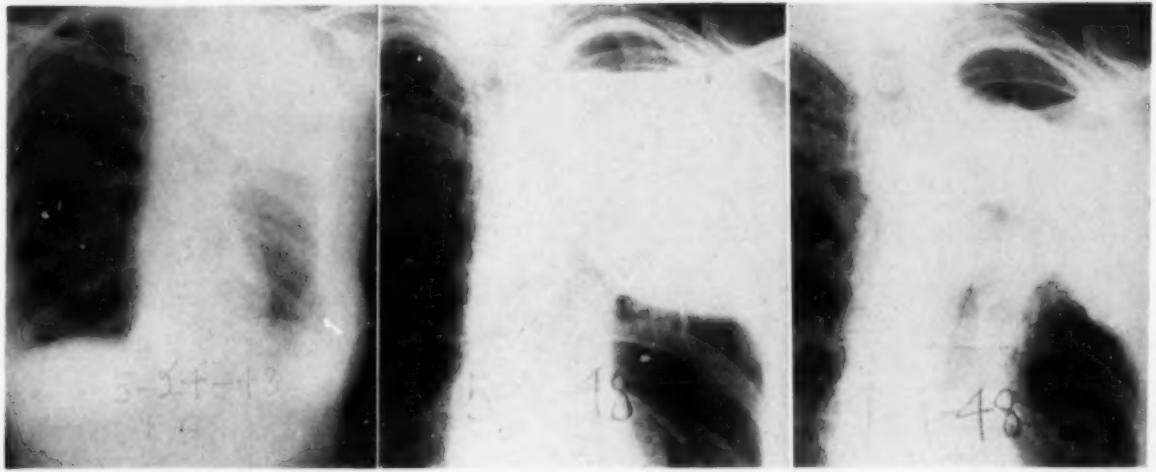

FIGURE 13 FIGURE 14 FIGURE 15

Figure 13, Case V: Roentgenogram showing leakage of contents of extrapleural space inferiorly and no evidence of active parenchymatous disease. Original film showed fluid level between pus and oil. — *Figure 14, Case V:* Roentgenogram made following partial aspiration of contents of extrapleural space with substitution of air; ½ cm. thick lining is prominent in apical portion of space.—*Figure 15, Case V:* Roentgenogram showing failure of obliteration of extrapleural space either by lung reexpansion or shift or fibrosis.

because many of these patients required conversion to oleothorax. Statements made regarding extrapleural pneumonolysis with paraffin filling are also applicable to extrapleural pneumothorax and oleothorax. Here again the indications were extended until the procedure found itself, for a time at least, in competition with thoracoplasty.[1,4,8,9,17,33,36] In their world survey in 1940 Dolley, Jones and Skillen[9] recognized the unquestionable inferiority of extrapleural pneumothorax as compared to thoracoplasty and concluded that the former was not indicated if the latter was feasible. As already pointed out by others,[3,5,10,22,24,26,36] extrapleural pneumothorax was proposed as a temporary and reversible collapse procedure for patients in whom intrapleural pneumothorax was indicated but was not feasible, yet it was often employed in patients requiring irreversible collapse. This procedure turned out to be not only permanent and irreversible in a large percentage of cases, but frequently also difficult to obliterate by any method.[22] Despite the statement of Dolley, Jones and Skillen in 1940[9] that from their personal experience and from the survey of the world literature it appeared that re-expansion of lung collapsed by extrapleural pneumothorax or oleothorax was very unlikely, others continued to refer to this procedure as temporary and reversible as late as 1946.[4,17]

A less common but real complication of extrapleural pneumothorax is air embolism; thus at Olive View Sanatorium[11] during the five-year period ending July 1, 1941 there were four instances of air embolism, one of which was immediately fatal, among extrapleural pneumothorax patients; during the same period of time among a very much larger number of intrapleural pneumothorax patients there were 15 instances of air embolism four of which were fatal. During the same period among the same patients there were three instances of bronchoextrapleural fistulae in the extrapleural pneumothorax patients as compared to 16 such fistulae in the intrapleural pneumothorax patients. Only one other report of fatal air embolism was encountered in the literature reviewed.[14]

In his book Alexander[2] predicted in 1937 that extrapleural pneumothorax was unlikely to find favor and that there was considerable risk of infection of the space. Following extensive application of the procedure abroad and in this country both predictions came true, at least in the United States.[3,5,10,20,21,22,24,26,28,29,32,36] In their critical survey of 1940 comprising about 2,500 cases collected from the world literature Dolley, Jones and Skillen[9] reported a mortality rate attributable to the operation of 8 to 17 per cent depending upon the type of patient selected for the operation. A review of the available English language literature

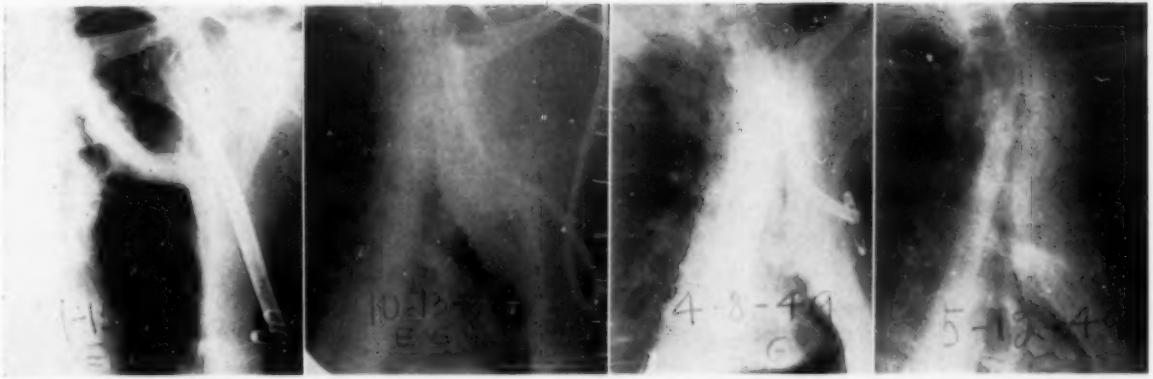

FIGURE 16 FIGURE 17 FIGURE 19 FIGURE 20

Figure 16, Case V: Roentgenogram following drainage of space by rib resection.—*Figure 17, Case V:* Roentgenogram showing residual extrapleural space with portions of the extrapleural "peel" retained.—*Figure 19, Case V:* Residual chest wall sinus persisting five months after drainage by rib resection.—*Figure 20, Case V:* Obliteration of residual sinus and permanent healing eight months after institution of surgical therapy.

on extrapleural pneumothorax published since 1940 (Table I) disclosed that in a total of 1,245 collected cases observed for from one-half to 11 years postoperatively the mortality rate attributable to the operation ranged from zero to 23 per cent, bronchoextrapleural and extrapleurocutaneous fistulae from zero to 14.5 per cent and extrapleural empyema from 5 to 40 per cent. The longer the period of postoperative follow-up the higher the incidence of complications. The danger of unrecognized infection of the extrapleural space is well exemplified by the following two patients treated for complications of extrapleural oleothorax.

Case IV: Figure 8 represents the 1940 roentgenogram, which is the latest preoperative one available, in the case of this 32 year old female who presented herself in August 1945 with the complaints of high fever, weakness, anorexia, weight loss and drainage of pus and food particles through the chest wall (Figure 9). Examination disclosed an acutely and chronically ill and emaciated individual with a left upper thoracoplasty and drainage of seropurulent secretions and food particles through several small openings in the operative scar. The history related by this patient dated back to 1937; as shown in the 1940 roentgenogram (Figure 8), left pneumothorax appeared to be effective despite restricting adhesions and was discontinued in April 1940 and right pneumothorax was induced. Progress was uneventful until 1942 when pulmonary hemorrhage of about a cupful took place; no roentgenograms of this period are available; left extrapleural pneumothorax was done in February 1942. The postoperative course was stormy with a maximum temperature of 105 degrees F.; extrapleural empyema and infection of the incision line developed early. Oleothorax was substituted for pneumothorax and her condition improved and remained satisfactory for about three years when in March 1945 she complained of high fever, pressure along the left side of the chest and neck, hoarseness and dyspnea; this was followed by the passage of a massive oily stool but no vomiting or expectoration of oil. The patient was rehospitalized, right pneumothorax was discontinued, the left extrapleural space was drained and antibiotic therapy was instituted. Six weeks later left upper thoracoplasty was done in an effort to obliterate the infected space; the operative incision healed but later following another febrile episode it broke down with the escape of food particles which has persisted off and on. When I first saw this patient an esophagoextrapleurocutaneous fistula was present; debridement of the wound to improve drainage and feedings through a Levine tube resulted in a slight and temporary improvement; she was then admitted to a public sanatorium where she expired soon after gastrostomy was performed; no autopsy was permitted.

Case V: Figure 10 represents the preoperative roentgenogram of a 44 year old female whose sputum was positive for tubercle bacilli and whose disease was predominantly unilateral and limited to the left lung where a 1 x 1.5 inch cavity was present at the level of the fifth rib posteriorly. The left pleural space was found to be obliterated and left extrapleural pneumothorax was perforemd in October 1938; following development of an effusion, conversion to oleothorax using 2½ per cent gomenol with 10 per cent lipiodol in olive oil was accomplished in September 1939 and she was discharged with a successful result in January 1940 (Figure 11). After 1944 tappings of the extrapleural space at regular intervals were discontinued. When she was referred to me on May 24, 1948, i.e., 10 years postoperatively, she had a slight dry cough, a low grade fever and a pale, fluctuating and non-tender subcutaneous swelling about six inches in diameter at the lower angle of the left scapula. The significant roentgenological findings (Figures 12 and 13) consisted of a soft tissue bulge posteriorly and evidence of leakage of the contents of the extrapleural space inferiorly; there was no evidence of tuberculous activity in the parenchyma. The original roentgenograms also showed a sharp horizontal fluid level

FIGURE 18, Case V: Extrapleural "peel" removed by digital decortication following redrainage of extrapleural space.

between the less opaque but more dependent collection of pus and the more opaque but lighter oily medium.

The soft tissue swelling was aspirated and incised and a mixture of oil and old blood was drained; aspiration of the extrapleural space anteriorly with the patient supine yielded dark oily material as the top layer and gray purulent fluid as the bottom layer. Figure 14 reveals the 0.5 cm. thick lining of the extrapleural space containing air, oil and pus. Following drainage of the soft tissue swelling it healed promptly and frequent aspirations of the extrapleural space were carried out with air-tight technique followed by instillation of Neoprontosil to keep the pus thin; this resulted in but a slight diminution in the size of the extrapleural space (Figure 15) despite efforts to produce pulmonary reexpansion over a three-month period. The fluid remained negative for tubercle bacilli and pyogens until August 1948 when it became thicker and non-hemolytic staphylococci were cultured from it. Surgical therapy was then embarked upon in the form of open dependent drainage by rib resection high in the axilla (Figure 16) followed by a one-stage posterolateral extrapleural thoracoplasty.

When a residual empyema cavity persisted with x-ray evidence (Figure 17) of retention of some of the fibrous lining of the extrapleural space, anterior thoracoplasty through a parasternal incision was done and at the same sitting the empyema was redrained through the previous site. The extrapleural space was found to contain plaques of leathery material up to 6 cm. in diameter and 0.5 cm. in thickness which resulted from the fracture of the eggshell-like lining of the extrapleural space by the thoracoplasty and which were not completely expelled following the first drainage of the extrapleural pyooleothorax (Figure 18). Histological examination of the extrapleural "peel" revealed hyalinized and partially calcified connective tissue with no evidence of tuberculosis.

Following redrainage of the extrapleural space and digital extrapleural decortication the residual empyema space was gradually reduced to a sinus (Figure 19) which persisted for five months discharging bits of "peel" but finally became obliterated one year after onset of empyema necessitans and eight months following institution of surgical therapy (Figure 20). Within a few days following the first drainage operation by rib resection superinfection of the extrapleural space with B. Pyocyaneus developed and despite treatment with streptomycin and penicillin topically and intramuscularly and acetic acid solution and sulfonamides topically, it persisted off and on almost throughout the entire period of drainage until healing was completed. At no time during the year of surgical therapy was there any evidence of tuberculous

activity clinically, bacteriologically or roentgenographically. The present condition of the patient is excellent as far as the pulmonary process and the extrapleural infection are concerned and she is working, but on exertion there is moderate dyspnea.

Comment: It appears that not every patient who expells the contents of the extrapleural space can be as lucky as Head's patient. In 1944 he told of one who after eight years of intrapleural oleothorax expectorated the oily contents of her pleural space but went on with pneumothorax refills without developing empyema.[13] The two patients with oleothorax reported here obviously were not given the after-care that would have established the diagnosis of infection before spontaneous perforation threatened or actually took place. However, this circumstance should not be utilized to absolve the surgical procedure of what appears to be its greatest weakness and danger, namely, the tendency to infection. These two cases illustrate what harm may result when patients suitable for thoracoplasty insist upon or are offered a supposedly reversible collapse procedure involving the creation of an artificial tissue space which is filled with a foreign substance. The thickness and rigidity of the extrapleural peel in Case V is the reason for the irreversible character of collapse by extrapleural pneumothorax and oleothorax if maintained for more than a brief period of time; the difficulty in obliterating such a rigid-walled space by thoracoplasty alone also becomes obvious.

Indications

The indications for extrapleural pneumonolysis and plombage are necessarily narrow and appear to be limited to two categories of patients:

1) As a temporary procedure preparatory to thoracoplasty or excisional surgery in children and adolescents in whom pneumothorax and pneumoperitoneum are not indicated or failed and in whom thoracic deformity resulting from thoracoplasty at this age is to be avoided and excisional surgery is contraindicated.

2) As a definitive procedure and a substitute for thoracoplasty in the elderly and in the presence of cardiac and/or pulmonary insufficiency due to asthma, emphysema or bilateral tuberculosis; the advantages are those of a single stage procedure which is reversible in the early postoperative period should the patient be unable to tolerate the reduction in pulmonary function resulting from pneumonolysis.

The choice of filling material depends on the extent of collpase; for limited apical collapse paraffin is more suitable, whereas in patients requiring a large extrapleural space pneumothorax and oleothorax are to be preferred. The sad experiences of Cases IV

and V illustrate the importance of close follow-up of patients with extrapleural filling as long as the filling is permitted to remain.

SUMMARY

1) Five cases of late complications of extrapleural pneumonolysis and plombage are presented; spontaneous discharge of the filling material with or without coexisting empyema was present in all and in one there was the rare complication of esophago-extrapleurocutaneous fistula.

2) Unless other therapeutic procedures are contraindicated it appears that in extrapleural pneumonolysis with plombage the patient is burdened with the danger of a serious late complication of the treatment superimposed on the risk of the primary disease itself.

3) Further restriction rather than extension of the application of this procedure in the therapy of pulmonary tuberculosis is being urged and indications for its employment are suggested.

Acknowledgments: The author is indebted to Drs. L. Tepper, M. Schiff and A. A. Cohen of the Los Angeles City Health Department and to Dr. C. E. Babcock, Medical Director, Olive View Sanatorium, for making available the records and roentgenograms of the cases presented.

RESUMEN

1) Se presentan cinco casos de neumonolisis con plombaje con complicaciones tardías. En todos ellos hubo eliminación del material de llenado con o sin empiema coexistente y en uno de ellos hubo una complicación rara consistente en fístula esofagoextrapleuro-cutanea.

2) A menos que haya contraindicación de otros procedimientos, cuando se reusa la neumonólisis con plombaje, el enfermo tiene el peligro de una complicación tardía además del riesgo de la enfermedad misma.

3) Se sugiere que se restrinja más aún el uso de este procedimiento en lugar de que se amplíe y se proponen las indicaciones para su uso.

RESUME

1) L'auteur présente cinq cas de pneumolyses extra-pleurales avec plombage pour lesquelles il y eut des complications tardives; il y eut dans tous les cas élimination spontanée de la substance de plombage avec ou sans pleurésie purulente. Dans un cas existait une complication rare: une fistule oesophago-extrapleurocutanée.

2) Sauf quand tout autre procédé therapeutique est contre-indiqué, la pneumolyse extra-pleurale avec plombage parait une méthode dangereuse. Il faut craindre de sérieuses complications

tardives, venant se superposer aux risques provenant de la maladie elle-même.

3) Il y aurait plutôt à envisager une diminution qu'une extension de l'utilisation de ce procédé thérapeutique dans la tuberculose pulmonaire. L'auteur en propose les indications.

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Local Thiosemicarbazone Therapy in Tuberculous Empyema*

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Several reports have appeared concerning the favorable effect of PAS and thiosemicarbazone locally in the treatment of tuberculous empyema. In a previous publication[1] from this institution we have reported the lack of effectiveness of PAS locally in the treatment of open draining empyema among tuberculous patients. This report concerns treatment of the same condition with thiosemicarbazone. A number of the same patients were used in both studies.

Method

All of the patients studied had long standing tuberculous empyema with mixed infection. Many had large bronchopleural fistulas; all had had rib resections with wide open drainage. The drainage material was frankly purulent in all cases and cultures revealed tubercle bacilli and other organisms. As in our previous study, the sizes of the empyema cavities were measured by filling with fluid before and after treatment, and by means of sinograms. These measurements could not be performed on some of the patients because of the large bronchopleural fistulas. Bacteriological tests were performed before and after treatment.

The patients were divided into two groups. In Group I the patients were treated with a daily instillation of 10 to 20 cc. of 10 per cent para-amino-salicylic acid suspension (not the sodium salt). Following the instillation, a large bandage was placed over the wound and the patient was urged to lie on the opposite side as long as possible. Treatment was continued for four months.

In Group II the instillation consisted of 200 mgm. of thiosemicarbazone dissolved in 10 cc. of propylene glycol, and was otherwise carried out as above.

Eight patients finished the four months of therapy in the first group. Six patients finished the course of therapy in the second group. Three others in each group received treatment for one to two months.

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Results

Slight thinning and diminution of the drainage was noted by several patients in each group. No notable change occurred in the clinical course of the patients treated. Those who had been improving prior to local therapy continued to do so and those who were going downhill continued on the same course. Measurements of the volume of the empyema cavities before and after treatment revealed little or no change. No significant differences could be noted between the PAS-treated group and the thiosemicarbazone-treated group.

Discussion

Dempsey and Logg;[2] Sivriere;[3] Gilliard;[4] and Carstensen[5] have given favorable reports on the local therapy of tuberculous empyema with PAS. Battke and Schroter[6] state that irrigation and instillation of thiosemicarbazone is the treatment of choice. Cuthbert,[7] on the other hand, found PAS no more effective than saline. Our own findings indicate that neither of these drugs has any significant effect.

The cause of these differences of opinion probably lies largely in the definition of the term "empyema." In our series, all patients had grossly purulent fluid; tubercle bacilli could be found on direct smear; and other pyogenic organisms were consistently present. Such cases obviously have empyema. However, some workers include under this term cases with clear fluid in which tubercle bacilli can be found only by culture. Some include cases with "cloudy" or "turbid" fluid without describing the cytology or bacteriology. It is self-evident that the prognosis is not the same under these various circumstances. Clearly, it is necessary that so-called empyema be described more accurately, with attention to the cytological and bacteriological findings in detail. Lack of a control series for comparison is another shortcoming in many of the reports. It is suggested that trial of a drug for empyema requires that an untreated group of similar cases be evaluated at the same time.

SUMMARY

Local instillations of 10 per cent PAS were given daily for four months to a group of patients with open draining mixed tuberculous empyema. A similar group of patients received 200 mgm. of thiosemicarbazone daily in 10 cc. of propylene glycol. No significant benefit was noted from either form of therapy.

RESUMEN

Durante cuatro meses se hicieron instilaciones locales de PAS al 10 por ciento a un grupo de enfermos con empiema abierto

canalizando. Un grupo similar de enfermos recibió 200 mg. de tiosemicarbazona diariamente en 10 cc. de propilen glicol. No se obtuvo beneficio alguno de ninguna de las dos formas terapeúticas.

RESUME

Un grupe de malades atteints de pleurésie purulente drainée à été traité par des instillations locales de P.A.S. à 10% chaque jour pendant quatre mois. Un grupe comparable de malades fut traité quotidiennement par 200 milligrammes de thiosémicarbazone dans 10 cc. de propylene glycol. Aucune de ces méthodes de traitement n'a permis de noter une action favorable.

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The Antibacterial Action of Citrus Peel Oil on the Tubercle Bacillus in Vitro*

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Citrus oil is a clear volatile oil with a pleasant pungent odor. The material furnished for these experiments was extracted from citrus peel and is double distilled. Citrus peel oil mixed with dehydrated gum turpentine in the proportions of 80 per cent and 20 per cent respectively, has been used commercially as a deodorant and an insect repellant. Because of its penetrating properties citrus oil has also been used as a carrier of coloring material for coloring citrus fruit and as a carrier of paraffin oil to prevent drying and shrinkage of citrus fruit.

It has been reported to us that in recent months individuals handling the citrus oil mixtures found that infected skin wounds and fungus infections of the skin responded well therapeutically when the mixtures were applied to the lesions. Because of these effects we became interested in testing the citrus oil-turpentine mixture and the citrus oil and turpentine separately for their possible bactericidal and fungicidal action.

Procedure

Preliminary tests were made by heavily seeding two Sabourands agar plates with Candida albicans. A ten millimeter well was made in the center of one of the plates and this was filled with the citrus oil-turpentine mixture. The second plate was used as the control plate. Another sterile plate was poured with Difco assay agar. This was thoroughly streaked with M. butyricum and one milliliter of the citrus oil-turpentine mixture was added and allowed to spread over the entire surface. A control plate was set up without the oil mixture. The above cultures were placed at 37 degrees for incubation and observations were made at the end of 48 hours. There was a 30 mm. ring of inhibition on the plate containing the 10 mm. well filled with the citrus oil-turpentine mixture and inoculated with C. albicans. There was no evidence

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of growth on the assay agar plate containing one milliliter of oil and seeded with M. butyricum. There was, however, abundant growth on both control plates.

Another experiment was performed in which one milliliter of the citrus oil-turpentine mixture was allowed to run over the surface of the media in a Lowenstein culture bottle which had been heavily seeded with a virulent strain of M. tuberculosis. A control bottle was set up without the oil mixture. After eight weeks incubation there was no evidence of growth on the Lowenstein culture media heavily seeded with M. tuberculosis and containing on its surface one milliliter of the citrus oil mixture. The control bottles showed abundant growth. At the time growth first appeared in the control bottles scrapings of the test culture containing the citrus oil mixture were transferred to fresh Lowenstein culture bottles. After six weeks of incubation there was no evidence of growth.

In an attempt to determine whether the growth inhibiting factor was in the citrus oil or in the turpentine the tests with Candida albicans and M. butyricum seeded on Sabourands media were repeated using one milliliter of citrus oil alone on one plate and one milliliter of turpentine on the other. Control plates were again set up for both Candida albicans and M. butyricum. There was an abundant growth on Candida albicans and M. butyricum after 48 hours in the control plates and in the plates where turpentine alone was used. There was no growth on the plates where citrus oil alone was used in 48 hours indicating the anti-growth factor was present in the citrus oil.

Further studies were made on a strain of S. aureus which had been isolated from an abscess. The 24 hour growth from three nutrient agar slants was washed off in the five milliliters of sterile saline. One-half milliliter of this growth suspension was placed into sterile tubes containing five milliliters of the following test solutions:

1) Citrus oil, 100 per cent.

2) Citrus oil, 80 per cent; Turpentine, 20 per cent.

3) Dehydrated gum turpentine, 100 per cent.

The test solutions were shaken well. At five, ten and fifteen minute intervals a loopful was transferred to nutrient agar slants. Control tubes were made by inoculating with a loopful of the saline suspension. The tubes were incubated at 37 degrees for 48 hours. After 24 hours and at the end of the 48 hour period growth was observed as indicated in Table I.

TABLE I

	Growth after 5	10	15 minute contact
Citrus oil, 100 per cent	+	−	−
Citrus oil, 80 per cent and Turpentine, 20 per cent	+	−	−
Turpentine, 100 per cent	+	+	+
Control	+	+	+

The same formulae above were tested employing nutrient broth. One-half milliliter of a 24 hour growth of S. aureus in broth was employed in each five milliliter portions of the mixture under test. The following results were obtained as indicated in Table II.

TABLE II

	Growth after 5	10	15 minute contact
Citrus oil, 100 per cent	−	−	−
Citrus oil, 80 per cent and Turpentine, 20 per cent	−	−	−
Turpentine, 100 per cent	+	+	+
Control	+	+	+

It should be noted that both the saline and broth suspension of organisms in the above experiments did not mix well with the test solutions. However, they were thoroughly shaken before the test loopful was transferred to the saline nutrient broth.

The following modification of the above technic was employed in testing the effects on M. tuberculosis. A small bacterial spatula with a blade 5 mm. in breadth was used to transfer approximately equal amounts of M. tuberculosis growth from a Lowenstein culture bottle to five milliliters of each respective test solution. This was thoroughly mixed with a glass rod. After five, fifteen and thirty minutes a loopful was transferred to Lowenstein media culture bottles. At the end of seven weeks the following observations were made as indicated in Table III.

TABLE III

	Growth after 5	10	15 minute contact
Citrus oil, 100 per cent	−	−	−
Citrus oil, 80 per cent and Turpentine, 20 per cent	−	−	−
Turpentine, 100 per cent	+	+	+
Control	+	+	+

Discussion

The findings in Table III indicate a marked inhibitory action of citrus oil on the growth of M. tuberculosis. The implications of our findings in the test tube are that citrus oil may have an antibacterial effect on the tubercle bacillus infecting humans. Plans are now in progress to study the possible toxic reaction and the possible antibacterial properties of citrus oil on the tubercle bacillus in animals before any attempts are made to test its possible effects in human tuberculosis.

SUMMARY

The antimicrobic effects of citrus peel oil on M. tuberculosis and other organisms have been demonstrated and the implications discussed. Experiments are now in progress to study the effects of citrus oil in animals.

RESUMEN

Los efectos antimicróbicos del aceite de la corteza de los citrosos en M. tuberculosis y otros organismos, han sido demostrados y sus implicaciones discutidas. Actualmente se están haciendo experimentos para estudiar los efectos del aceite de los citrosos en los animales.

Plans Completed for Important World Congresses

Two important World Congresses will be held in Rio de Janeiro, Brazil, August 24-30, 1952. For the first time, the II International Congress on Diseases of the Chest sponsored by the Council on International Affairs of the American College of Chest Physicians will be held in conjunction with the XII Congress of the International Union Against Tuberculosis. Last year, the International Union Against Tuberculosis met in Copenhagen, Denmark, and a week later, the Council on International Affairs of the American College of Chest Physicians held a Congress on Diseases of the Chest in Rome, Italy. Both of these Congresses were well attended, and it is anticipated that a record number of chest physicians from all over the world will convene in Rio de Janeiro in August of 1952 for both Congresses.

The latest advances in the treatment and control of tuberculosis, as well as non-tuberculous chest diseases will be presented by prominent authorities in the specialty. Physicians wishing to present manuscripts on *tuberculosis* should prepare abstracts not to exceed 100 words and forward them to:

Dr. Etienne Bernard, General Secretary
International Union Against Tuberculosis
47 Rue de Courcelles
Paris, France.

Physicians wishing to present manuscripts on *non-tuberculous* diseases should prepare abstracts not to exceed 100 words and forward them to:

Dr. Andrew L. Banyai, Chairman
Council on International Affairs
American College of Chest Physicians
112 East Chestnut Street
Chicago 11, Illinois.

An interesting social program is also being planned for physicians and their wives in beautiful Rio de Janeiro. At the close of the Congress in Rio de Janeiro, physicians will be given an opportunity to visit Sao Paulo and many other interesting Brazilian cities.

Physicians who plan on attending the Congresses should write at once for complete information concerning hotel accommodations and transportation to:

Executive Offices
American College of Chest Physicians
112 East Chestnut Street
Chicago 11, Illinois.

(See advertising page xii).

CENTRAL BRAZILIAN CHAPTER INAUGURATES TWO WORLD CONGRESSES TO BE HELD IN RIO DE JANEIRO, AUGUST 24 - 30, 1952

A meeting of the Central Brazilian Chapter was held on August 30, 1951, to discuss plans for the XII Congress of the International Union Against Tuberculosis, and the II International Congress on Diseases of the Chest sponsored by the Council on International Affairs of the American College of Chest Physicians. Dr. Affonso MacDowell, Regent for Brazil, presided at the meeting, and introduced Dr. Manoel de Abreu, President of the Central Brazilian Chapter and President of the two World Congresses, who together with Dr. Reginaldo Fernandes, Governor for the Central Brazilian Chapter and Secretary General for the World Congresses, discussed the preliminary plans for both Congresses to be held in Rio de Janeiro, August 24-30, 1952. Mr. Murray Kornfeld, Executive Secretary of the American College of Chest Physicians, was introduced and pledged the support of the College to both Congresses. He also discussed College activities throughout the world. The meeting was attended by Doctor Jose Rosemberg of Sao Paulo, Governor for Southern Brazil, who extended an invitation to the participants of the Congress to meet in Sao Paulo following the close of the sessions in Rio de Janeiro next August. A business meeting was held at which the following officers were elected for the Central Brazilian Chapter:

Dr. Manoel de Abreu, President

Dr. Arlindo de Assis, Vice-President

Dr. Ugo Pinheiro Guimaraes, Vice-President

Dr. Affonso Mac Dowell Filho, Secretary

Dr. Joao Castello Branco, Treasurer.

GETULIO VARGAS, PRESIDENT OF BRAZIL, ACCEPTS HONORARY CHAIRMANSHIP FOR THE 1952 WORLD CONGRESSES

Reading from left to right: Hon. Getulio Vargas, President of Brazil; Professor Manoel de Abreu, President, Central Brazilian Chapter, and President of the World Congresses; Mr. Murray Kornfeld; Dr. Aresky Amorim, Professor of Surgery, University of Brazil; Dr. Ugo Pinheiro Guimaraes, President, Brazilian Tuberculosis Association; Dr. Antonio Ibiapina, Professor of Tuberculosis, University of Brazil; Dr. Reginaldo Fernandes, Director of Tuberculosis, Federal District of Brazil, and Secretary General of the World Congresses; and Dr. Pereira Filho, Member, Committee on Organization.

The Honorable Getulio Vargas, President of Brazil, received a delegation of prominent Brazilian physicians at the "Palacio do Catete," Presidential Palace, Rio de Janeiro, on September 4, 1951. President Vargas is being congratulated upon his acceptance of the Honorary Chairmanship for the XII Congress of the International Union Against Tuberculosis, and the II International Congress on Diseases of the Chest sponsored by the Council on International Affairs of the American College of Chest Physicians. The members of the Council are as follows:

Andrew L. Banyai, Wisconsin, Chairman

Council on Pan American Affairs
Richard H. Overholt, Massachusetts
Chairman
Raul F. Vaccarezza, Argentina
Vice-Chairman
Juan R. Herradora, New Jersey
Secretary

Council on European Affairs
Paul H. Holinger, Illinois
Chairman
Gustav Maurer, Switzerland
Vice-Chairman
Richard R. Trail, England
Secretary

Council on Pan Pacific Affairs
Seymour M. Farber, California
Chairman
Miguel Canizares, Philippines
Vice-Chairman
Forrest J. Pinkerton, Hawaii
Secretary

Council on African and Eastern Affairs
Edgar Mayer, New York
Chairman
Moses J. Stone, Massachusetts
Vice-Chairman
Basil A. Dormer, South Africa
Secretary

CHILEAN CHAPTER MEETING

The members of the Chilean Chapter in Valparaiso met for luncheon at the Naval Club, Valparaiso, Chile on August 1, 1951, to discuss plans for their participation in the Two World Congresses to be held in Rio de Janeiro, August 24-30, 1952. Other College activities including plans for Resident College Fellowships were also discussed at the meeting.

ARGENTINE CHAPTER MEETING

On August 20, 1951, a dinner meeting arranged by Prof. Raul Vaccarezza, Governor of the College for Argentina, was given at La Cabana, Buenos Aires, Argentina. The Argentine Chapter Officials discussed plans for Resident College Fellowships and the Two World Congresses to be held in Rio de Janeiro, August 24-30, 1952.

HONORARY MEMBERSHIP IN BRAZILIAN TUBERCULOSIS ASSOCIATION AWARDED EXECUTIVE SECRETARY OF THE COLLEGE

Reading from left to right: Dr. Ugo Pinheiro Guimaraes, President of the Brazilian Tuberculosis Association, and Vice President of the Central Brazilian Chapter; Dr. Reginaldo Fernandes, Governor, Central Brazilian Chapter; Dr. Affonso MacDowell, Regent for Brazil; Mr. Murray Kornfeld, Executive Secretary of the College; Dr. Manoel de Abreu, President, Central Brazilian Chapter; Dr. Antonio Ibiapina, Professor of Tuberculosis, University of Brazil; and Jose Rosemberg, Governor for South Brazilian Chapter.

Upon accepting this honorary membership in the Brazilian Tuberculosis Society, Mr. Kornfeld replied as follows:

"The Board of Regents and the Council on International Affairs of the American College of Chest Physicians have sent me, as their ambassador, to discuss with you our mutual problems.

"It is regrettable that all of the members of the Congress could not be here tonight to participate in this impressive ceremony, to witness the fine spirit of cooperation, and to feel that warm friendliness which pervades this assembly.

"Last year in the city of Rome, we held our First International Congress. Those of you who joined the physicians from forty-two countries who attended the Congress, must have been impressed with the good will engendered by this first Congress. We gave conclusive proof in Rome that men of good will with varied customs and with different political opinions could meet and discuss sincerely and without bias, problems concerning the health and welfare of their people.

"Next year physicians from all parts of the world will gather in the beautiful city of Rio de Janeiro to participate in two important scientific assemblies. For the first time two important world organizations, the International Union Against Tuberculosis and the American College of Chest Physicians, will meet jointly and present a unified attack against

disease. It is this type of mutual understanding which is so sorely needed today in a world groping for the solution of many difficult problems.

"Scientists will convene in Rio de Janeiro next year with but one thought and one purpose—to eradicate disease, wherever it exists. This is a noble purpose, and therefore, it gives me much pleasure to accept this honorary membership in the Brazilian Tuberculosis Association which you have so graciously bestowed upon me tonight."

URUGUAYAN CHAPTER MEETING

A dinner meeting arranged by Prof. Fernando Gomez, Regent of the College for Uruguay, was held at the Academy of Medicine, Montevideo, Uruguay, on August 24, 1951. Plans for the XII Congress of the International Union Against Tuberculosis and the II International Congress on Diseases of the Chest to be held in Rio de Janeiro, August 24-30, 1952, were discussed. Resident Fellowships and other activities of the Council on International Affairs of the College were also discussed.

FOURTH BIENNIAL CONFERENCE OF THE COUNCIL ON PAN AMERICAN AFFAIRS OF THE AMERICAN COLLEGE OF CHEST PHYSICIANS, GUAYAQUIL, ECUADOR, JULY 18, 1951

Fifty-two delegates and observers attended the Fourth Biennial Conference of the Council on Pan American Affairs of the American College of Chest Physicians held in conjunction with the IX Biennial Congress of the Pan American Union Against Tuberculosis (U.L.A.S.T.), which convened in Guayaquil under the Presidency of Dr. Jorge A. Higgins, July 14-22, 1951.

Among the officials of the Council on Pan American Affairs present at the Conference were: Dr. Chevalier L. Jackson, President, American College of Chest Physicians; Dr. Gumersindo Sayago, Regent for Argentina; Dr. Raul F. Vaccarezza, Governor for Argentina; Dr. Antonio Brown, Governor for Bolivia; Dr. H. Orrego Puelma, Regent for Chile; Dr. Carlos Arboleda Diaz, Regent for Colombia; Dr. Rafael J. Mejia C., Governor for Colombia; Dr. Juan Tanca Marengo, Regent for Ecuador;

Dr. Jorge A. Higgins, Governor for Ecuador; Dr. Enrique Coronado Iturbide, Governor for Guatemala; Dr. Miguel Jimenez, President, Mexican Chapter; Dr. Amadeo Vicente Mastellari, Panama, Regent for Central America; Dr. Fernando D. Gomez, Regent for Uruguay; Dr. Alejandro C. Artagaveytia, Secretary, Uruguayan Chapter; Dr. Jose Ignacio Baldo, Regent for Venezuela; Dr. Paul H. Holinger, Chairman, Council on European Affairs; Dr. Leo Eloesser, Member, Council on Pan American Affairs; and Mr. Murray Kornfeld, Executive Secretary, American College of Chest Physicians.

Observers at the Conference were Dr. Floyd M. Feldman and Dr. Herbert L. Mantz, representing the National Tuberculosis Association, and Dr. Esmond R. Long, representing the American Trudeau Society.

College Chapter News

KENTUCKY CHAPTER

At its annual meeting held at the Brown Hotel, Louisville, Kentucky, on October 4, 1951, the Kentucky Chapter of the College elected new officers. Twenty-eight physicians and guests attended the meeting presided over by Dr. R. O. Joplin, outgoing President of the Chapter. Dr. Julian Johnson, Professor of Surgery at the University of Pennsylvania School of Medicine, was guest speaker and spoke on the "Philosophy of Chest Tumors." The new officers are:

Hugh L. Houston, Murray, Kentucky, President
E. R. Gernert, Louisville, Kentucky, Vice President
Lawrence A. Taugher, Louisville, Kentucky, Secretary-Treasurer.

SOUTHERN CHAPTER

The Eighth Annual Meeting of the Southern Chapter of the College was held at the Adolphus Hotel, Dallas, Texas, November 4 and 5, 1951. An informative scientific program was presented. Lt. Colonel Frederic J. Hughes of Denver, Colorado, Dr. David T. Carr of Rochester, Minnesota, and Dr. Maurice S. Segal of Boston, Massachusetts, were among the guest speakers on the program. Dr. M. Jay Flipse of Miami, Florida, retiring president, delivered an interesting address on "These Changing Times." Dr. H. Frank Carman and Dr. John Chapman, both of Dallas, Texas, were in charge of arrangements for the meeting. A tribute was paid to Dr. George R. Hodell of Houston, Texas, for his excellent services as Secretary-Treasurer of the Southern Chapter for 1951.

Plans for the Second Annual Postgraduate Course sponsored by the Council on Postgraduate Medical Education and the Southern Chapter of the College were discussed at the meeting. This course will be held in Houston, Texas under the Chairmanship of Dr. Alvis E. Greer, a member of the Council on Postgraduate Medical Education.

The following officers were elected to serve during the coming year:

Hollis E. Johnson, Nashville, Tennessee, President
Duane Carr, Memphis, Tennessee, First Vice-President
John S. Harter, Louisville, Kentucky, Second Vice-President
Alfred Goldman, St. Louis, Missouri, Secretary-Treasurer.

INDIANA CHAPTER

A luncheon meeting of the Indiana Chapter of the College was held at the Athenaeum, Indianapolis, Indiana, October 29, 1951. Thirty-five members and guests attended this meeting which was presided over by Dr. Paul D. Crimm of Evansville. The following scientific program was presented:

"Report of a Case of Pulmonary Histoplasmosis,"
James H. Stygall, Indianapolis, Indiana.

"Tuberculosis of the Bone,"
Reid Keenan, Indianapolis, Indiana.

"Adenomatosis of the Lung,"
William M. Tuttle, Detroit, Michigan.

An election of officers was then held at which the following were elected:

Thomas R. Owens, Muncie, Indiana, President
John N. Ewbank, Richmond, Indiana, Vice-President
Hubert B. Pirkle, Rockville, Indiana, Secretary-Treasurer.

Hubert B. Pirkle, Secretary.

NORTH CAROLINA CHAPTER

On Wednesday, October 31, 1951, the North Carolina Chapter of the College held its Second Annual Meeting. The afternoon session was held at the Veterans Administration Hospital, Oteen, North Carolina, and the evening session took place at the Battery Park Hotel in Asheville, North Carolina. (The complete program appeared in the September issue of *Diseases of the Chest*). Following the interesting scientific sessions, an election was held at which the following officers were elected:

James Mathews, Oteen, North Carolina, President
Verling K. Hart, Charlotte, North Carolina, Vice-President
Leon H. Feldman, Asheville, North Carolina, Secretary-Treasurer.

Leon H. Feldman, Secretary.

III PAN-AMERICAN CONGRESS OF OTO-RHINO-LARYNGOLOGY AND BRONCHO-ESOPHAGOLOGY

This Congress will be held in Havana, Cuba, on January 20-24, 1952. Dr. Chevalier L. Jackson, President of the American College of Chest Physicians, has been appointed as "Guest of Honor" of the Cuban Society of Oto-Laryngology. Dr. Jackson will give a lecture on "Technics of Peroral Endoscopy with a Special Consideration of Anatomical Factors," and Dr. Paul H. Holinger, Chairman of the Committee on Motion Pictures of the American College of Chest Physicians, will lecture on "Diagnosis and Treatment of Acute Laryngeal Dispnea in the Infant." Other members of the College on the program are Drs. Felix E. Leborgne and Julio Cesar Baroni of Uruguay, and Dr. Ricardo Tapia Acuna of Mexico.

Reservations for this meeting may be made by contacting Dr. Pedro Hernandez Gonzalo, General Secretary, 8 No. 358, Vedado, Havana, Cuba.

1952 ANNUAL PROGRAM

Physicians interested in presenting their work on the Program of the 18th Annual Meeting of the American College of Chest Physicians to be held at the Congress Hotel, Chicago, Illinois, June 5-8, 1952, should submit titles and abstracts of their material not to exceed 100 words to Dr. Harold G. Trimble, 2930 Summit Street, Oakland, California, Chairman of the Committee on Scientific Program of the College.

SAN FRANCISCO POSTGRADUATE COURSE

A postgraduate course in diseases of the chest under the sponsorship of the Council on Postgraduate Medical Education and the California Chapter of the American College of Chest Physicians, and the California Academy of General Practice will be held in cooperation with the University of California and Stanford University Schools of Medicine. The course will be held on four successive Wednesday afternoons and Wednesday evenings beginning January 16, 1952. The other dates will be January 23, 30 and February 6, 1952. The course will offer 25 hours of formal credit approved towards the postgraduate medical education requirements of the American Academy of General Practice, and will also be of interest to physicians specializing in chest diseases.

For reservations and further information please contact Dr. Stacy R. Mettier, Professor of Medicine, Head of Postgraduate Instruction, Medical Extension, University of California Medical Center, San Francisco 22, California.

College News Notes

The Department of Surgery at the University of Illinois College of Medicine has announced the promotions of Dr. Minas Joannides, Treasurer of the College, from Assistant Professor to Associate Professor, and Dr. Philip Thorek from Clinical Assistant Professor to Clinical Associate Professor.

Dr. Sotero del Rio Gundian, formerly Minister of Health for Chile, is visiting the United States under the auspices of the U. S. State Department to observe the latest methods in the management and treatment of chest diseases. With the cooperation of the Executive Offices of the College, some of the institutions visited by Doctor del Rio were: the Chicago Municipal Tuberculosis Sanitarium, Hines Veterans Administration Hospital, Winfield Sanitarium and the University of Illinois Medical Center. He attended the postgraduate course in diseases of the chest in New York City, and then visited the Trudeau Sanatorium at Saranac Lake and the Overholt Clinic in Brookline, Massachusetts.

At the 45th Annual Meeting of the Southern Medical Association held in Dallas, Texas, November 5-8, 1951, the following Fellows of the College presented papers:

Louis L. Friedman, Birmingham, Alabana,
"Anthracosilicosis (Miner's Asthma)."

John S. Chapman, Dallas, Texas,
"Infarction of the Lung."

Francis H. Cole, Memphis, Tennessee,
"Bronchiectasis: Clinical and Pathological Variations and Concepts of Pathogenesis."

Dr. Friedman received Second Award for his exhibit on Anthracosilicosis.

COURSE IN BRONCHO-ESOPHAGOLOGY

The next course in Broncho-Esophagology will be given February 11-22, 1952. For application forms and further information please communicate with the Department of Broncho-Esophagology, Lab 604, Temple University School of Medicine, 3400 N. Broad St., Philadelphia 40, Pa.

Chevalier Jackson and Chevalier L. Jackson.

FELLOWSHIPS IN INDUSTRIAL MEDICINE

The Institute of Industrial Health of the University of Cincinnati will accept applications for a limited number of Fellowships offered to qualified candidates who wish to pursue a graduate course of instruction in preparation for the practice of Industrial Medicine. Any registered physician, who is a graduate of a Class A medical school and who has completed satisfactorily at least two years of training in a hospital accredited by the American Medical Association may apply for a Fellowship in the Institute of Industrial Health. (Service in the Armed Forces or private practice may be substituted for one year of training). Requests for additional information should be addressed to the Institute of Industrial Health, College of Medicine, Eden and Bethesda, Cincinnati 19, Ohio.

MORTALITY STATISTICS ON CHILDREN

Vital statistics now available reveal that deaths from heart disease and cancer among children of school age exceed in number the deaths from all infectious and parasitic diseases combined, it was announced by the Federal Security Agency. Actually, there has been an overall decline in the number of all deaths from diseases in childhood, including those due to both heart disease and cancer. But the decline in the infectious and parasitic diseases has been overwhelmingly greater. This can be attributed for the most part to the antibiotics and improved measures for detecting and preventing these diseases. In 1948, the latest year for which complete figures are available, the study made by the National Heart Institute of the National Institute of Health, Public Health Service, revealed cardiovascular disease and cancer deaths—with rheumatic heart disease and leukemia the leading causes—totaled 4,514 in the 5 to 19 age group. In comparison, the infectious and parasitic—with tuberculosis the chief cause of death—accounted for 3,990 deaths in the same age group. Accidents, however, were the leading cause for all deaths in this age group, totaling 11,348 in 1948.

ANNOUNCEMENT

Because of increased mailing and production costs, the Editorial Board has found it necessary to increase the subscription rates to countries outside of the United States to $10.00 per year, effective January 1, 1952.

COLLEGE EVENTS

18th Annual Meeting, American College of Chest Physicians, Congress Hotel, Chicago, Illinois, June 5-8, 1952.

San Francisco Postgraduate Course,
January 16, 23, 30 and February 6, 1952.

XII International Union Against Tuberculosis and II International Congress on Diseases of the Chest,
Rio de Janeiro, Brazil, August 24-30, 1952.

MEDICAL SERVICE BUREAU

POSITIONS AVAILABLE

Medical director wanted for 100 bed tuberculosis hospital, southern state, North American graduate, $7,000 per year and complete maintenance. Please address Box 238A, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Assistant medical director wanted for 100 bed tuberculosis hospital, southern state, salary range to $6,500 per year and complete maintenance. Please address Box 239A, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Resident or staff physician wanted for 100 bed tuberculosis hospital 70 miles from Sun Valley, Idaho. Excellent facilities for medical and surgical treatment of chest diseases. Salary comensurate with training and experience, full maintenance provided. Graduate of American school and eligible for Idaho license required. Position under State Merit System. Please address Box 240A, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Applications are invited for positions of Resident and Assistant Resident at Grace Dart Home Hospital, 6085 Sherbrooke Street, East, Montreal. This is a 145 bed tuberculosis hospital, approved by the American College of Surgeons, and covers all aspects of medical and surgical treatment. Duties to commence July 1, 1952. Apply to Medical Director.

Staff physicians. Modern 380 - bed tuberculosis hospital. Metropolitan area. Man or woman acceptable, must be U. S. citizen, graduate of approved school. eligible for Ohio license. Salary depends on training—up to $6,000 plus maintenance. Address Box 236A, American College of Chest Physicians, 112 East Chestnut St., Chicago 11, Ill.

Physicians, Psychiatrists, and Tuberculosis Control Physicians are being offered immediate civil service employment with the State of Illinois through oral examinations or interviews. State residence is not necessary. Application forms may be obtained from the Illinois Civil Service Commission, Armory Bldg., Springfield, Ill.

POSITIONS WANTED

Physician desires residency in tuberculosis medical service. Hospital or sanatorium. Previous training in tuberculosis. Rotating internship. Please

address Box 260B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Chest specialist interested in private practice as an associate. Well trained and experienced. Class "A" American school graduate. Native born. Now holding a position of responsibility. References are outstanding. Please address Box 259B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Experienced and well trained chest specialist desirous of appointment as medical director or assistant medical director of a tuberculosis hospital. Now holding a responsible position, but contemplating change. Outstanding references. Class "A" American school graduate and native born. Please address Box 258B, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

ACTHAR

Acthar, the Armour Laboratories brand of ACTH, pituitary adrenocorticotropic hormone, has been accepted by the Council on Pharmacy and Chemistry of the American Medical Association. Thomas E. Hicks, vice-president of Armour and Company in charge of The Armour Laboratories of Chicago, announced that Armour's Lyophilized Acthar has been accepted for use in collagen disease or connective tissue diseases, such as rheumatoid arthritis, rheumatic fever, acute lupus erythematosus, hypersensitivities, most acute inflammatory diseases of the eye, contact dermatitis, acute inflammatory conditions of the skin, such as pemphigus and exfoliative dermatitis, and metabolic diseases such as acute gouty arthritis, and secondary adrenal cortical hypofunction.

COMPENAMINE

An entirely new salt of penicillin G, Compenamine, has been announced by C.S.C. Pharmaceuticals, a division of Commercial Solvents Corporation. The outstanding characteristic of Compenamine is its remarkably low allergenicity. It produces the same high plasma levels, but these levels are more prolonged, since Compenamine is considerably less water-soluble. An added advantage is that Compenamine is not attended by any hazard of cross sensitization, as it is an entirely new salt, not merely a variation of the penicillin mold. Compenamine is available in aqueous suspension (ready for injection), in oil, and in dry form for aqueous suspension.

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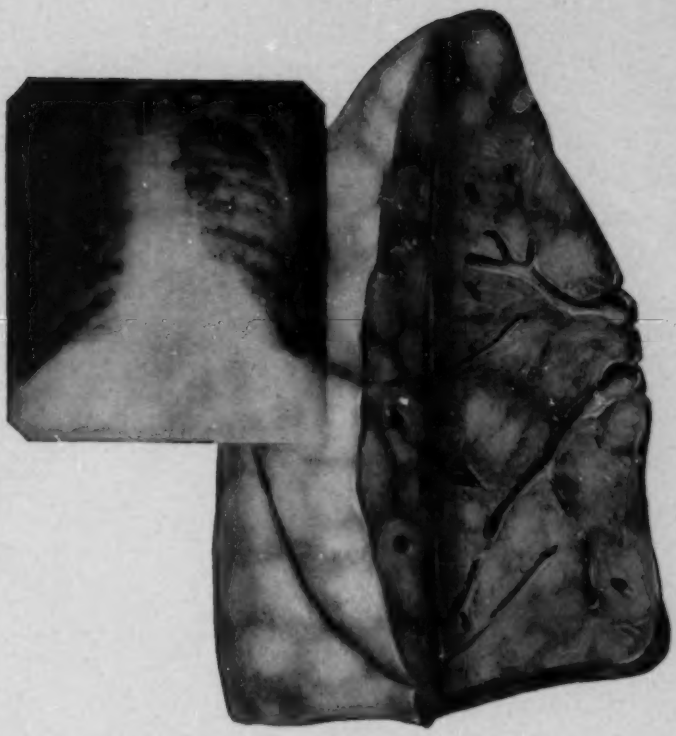
Jay Arthur Myers, M.D., F.C.C.P., Chairman, Editorial Board.



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Potterfield, T. C., and Starkweather, G. A.: J. Philadelphia General Hosp. 2:6 (Jan.) 1951.

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*TEMPEL, C. W., FREDERIC, J. H. Jr., MARDIS, R. C., TOWBIN, M. N., and DYE, W. E. Combined intermittent regimens employing streptomycin and PAS. Am. Rev. Tuberc., 1951, 63, 295

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